THE KIDNEY

An Outline of Normal and Abnormal Structure and Function

By

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With 74 Illustrations



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To

B. E. MILES

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PREFACE

THE purpose of this book is to present an outline of renal function and structure of the normal and diseased kidney. It is intended for students, but I hope it may also be useful to others who wish to know more about the subject.

At the beginning there is a short description of normal structure and function, and the methods used to obtain information about each are discussed. There then follows a description of the four main syndromes which occur in renal disease, i.e. the nephrotic syndrome, acute renal failure, chronic renal failure, and the acute nephritic syndrome, there is also a section on the relationship between disturbances of renal function and electrolyte disorders. The second half of the book consists principally of an account of renal diseases, including the renal manifestations of some generalised diseases. These are discussed in terms of the patterns of functional disturbance which have been described in the previous sections. Unless, therefore, the reader is already familiar with the subject it is best that he should start at the beginning or at least read the sections on the four syndromes and electrolyte disturbances before those on specific renal disorders.

For the sake of clarity, I have to confess that I have over-simplified many controversial subjects and in some instances given only one explanation where several exist. I have not attempted a comprehensive classification of renal disease, for in the present state of knowledge I doubt whether it is possible to arrive at a classification whose subdivisions are at the same time mutually exclusive and collectively exhaustive. Renal tuberculosis, hydronephrosis, calculi, renal tumours and certain other predominantly surgical conditions have been excluded.

I am indebted to the many workers and writers who have preceded me and I should like particularly to mention the following sources of information; Homer Smith's textbooks of renal physiology, A. C. Allen's histological textbook, "The Kidney", A. M. Fishberg's "Hypertension and Nephritis"; T. Addis' "Glomerular Nephritis"; R. W. Lippman's "Urine and the Urinary Sediment", G. W. Pickering's "High Blood Pressure", and, finally, J. R. Robinson's lucid "Reflections on Renal Function," which anyone interested in the kidney should read at least once. As a guide to more detailed reading there is a list of references at the end of each section.

I am grateful to Drs. B. E. Miles, R. R. McSwiney, D. M. Nut-

bourne, F. del Greco, R. D. Grainger, A. Herxheimer, Mr. K. E. D. Shuttleworth, Mr R D. de Vere, and Miss I. Maureen Young for their generous help with the manuscript and for giving me the benefit of their advice. I am also indebted to Drs A. C. Dornhorst and M. S. R. Hutt, and Mr M. Williams for their most helpful comments and for scrutinising the proofs I wish to thank Miss J. Dewe and Miss P. Leicester for the patience and care with which they drew Figs. 1, 2, 4, 5, 6, 71 to 74, and Figs 51, 53 to 60, and 68, respectively, and Mr. A L Wooding and Mr. B Kentish for the photographs of the figures. I am also glad to acknowledge the help of Mr. F. A. Tubbs, Miss M. E. Warner, Miss M. Matthews and Miss M. Studart in checking the references, and that of Miss J. Buchanan for her investigations on my behalf.

I am indebted to Drs. W J. Griffiths, R. R. McSwiney, J. R. Colley and W W. Holland for Figs. 9 and 38

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1

THE STRUCTURE OF THE KIDNEY

A KIDNEY contains about 1,000,000 nephrons Each nephron is a thin tube approximately 20–50 μ wide and 50 mm. long with one end closed and the other opening into a collecting duct. The total length of the tubules in the two kidneys is about 70 miles, or more than [illegible] r end of [illegible] a cluster [illegible] tube is

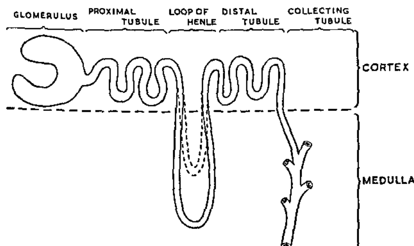


FIG 1 Schema of the structure of the nephron and its distribution between the cortex and medulla

coiled into a compact mass (the proximal tubule); it then plunges straight towards the hilum of the kidney, sometimes reaching into the medulla for a variable distance; it turns back in a tight hairpin bend (the loop of Henle) and once again lies in a coil (the distal tubule) next to its own glomerulus. Finally it straightens out and together with several other distal tubules joins a collecting duct, either in or near the medulla. Several collecting ducts join together and empty their contents into larger tubes called the papillary ducts which open directly on the surface of the pyramids (Fig 1).

Most of the proximal and distal tubules lie in the cortex, while the loops of Henle and the collecting ducts form the bulk of the medulla.

Glomerular Structure

The glomerulus is composed of 4–6 capillary loops which spring from the afferent arteriole and end in the efferent arteriole; they lie within a space whose peripheral wall is known as the glomerular capsule (or Bowman's capsule). This cluster of capillaries shares a stalk of endothelial cells; the cytoplasm of the outer part of the stalk is hollowed out to form the lumens of the capillary loops, while the inner part contains the nuclei (Fig. 2). There does not appear to be

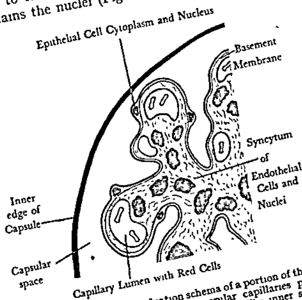


FIG. 2. Glomerulus. High magnification schema of a portion of the glomerulus to show that the lumens of the glomerular capillaries penetrate the periphery of a syncytium of endothelial cells. The inner surface of the capillary is formed from a prolongation of endothelial cell cytoplasm while the peripheral outer surface is covered by epithelial cell cytoplasm; basement membrane lies between.

any intercapillary substance, the central core of endothelial cells forming one continuous syncytium. The capillary loop is covered by a basement membrane which is continuous with that of the glomerular capsule and of the tubule; the glomerular capillary basement membrane is itself covered by a layer of epithelial cells (Fig. 3). The latter are a continuous extension of the cells of the proximal tubule and the glomerular capsule. The surface area of the loops of the glomeruli in both kidneys is about 1·5 square metres.

Electron microscopy has demonstrated that the cytoplasm of the

helial cells is divided peripherally into numerous thin extensions, that these lie in contact with the basement membrane covering the llary loops. The surface of the loops is therefore covered by a vast nber of interdigitating processes between which there are potential ces (Fig. 3). This is an arrangement which would seem to permit a atively large area of basement membrane to be exposed directly to e lumen of the capsular space which would not be possible if

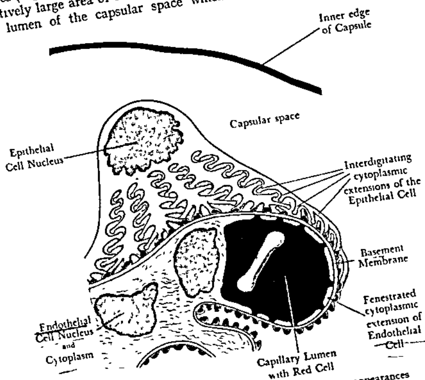


Fig 3 Glomerulus Schema of the electron microscopy appearances of a cross-section of a single glomerular capillary.

instead, the loops were covered by a thin, flat continuous layer of cytoplasm Electron microscopy has also shown that the cytoplasm of the endothelial cells, where it forms the inner surface of the capillary loops, is pierced by relatively large holes about 0 1 μ wide There is also some equivocal evidence that there are smaller apertures (100 Å) in the basement membrane. It is possible therefore that glomerular filtrate may pass directly from the lumen of the capillary into that of the capsular space without diffusion being necessary

Structure of the Tubule

The outer surface of the whole nephron is covered by a continuous layer of basement membrane. The proximal tubule is composed of irregularly cuboidal cells with coarse granular cytoplasm and ragged inner margins (the brush border) The cells of the loops of Henle are

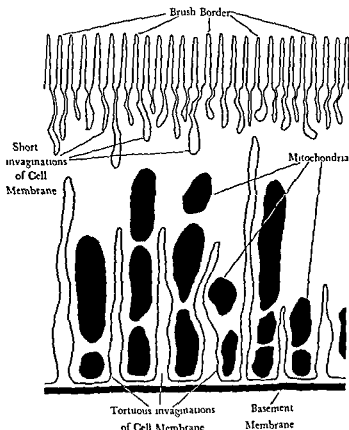


FIG 4 Tubule Schema of the electron microscopy appearances of a proximal tubule cell, the nucleus has been omitted

extremely thin and flat and have clear cytoplasm. The length of the loops varies greatly; those that originate from glomeruli near the cortico-medullary junction are the longest and penetrate deeply into the medulla The cells of the distal tubules are cuboidal but they are smaller than those in the proximal tubules; they have clear cytoplasm and sharp margins

With the electron microscope the brush border of the proximal

tubule cells is seen to consist of multiple projections of cell cytoplasm covered by surface membrane. Between these projections invaginations of the surface membrane penetrate into the cell cytoplasm and extend towards the mitochondria. These projections and invaginations increase enormously the area of contact between the tubular fluid and the contents of the cells. The membrane of the surface which lies next to the peritubular venous capillaries is also invaginated into a number of pockets which lie between the basal mitochondria (Fig. 4)

Cortico-medullary Junction

At the junction of the cortex with the medulla there is a thick, wide-meshed fibrous net to which the renal pelvis is attached and through which the medulla and pyramids project The vessels and lymphatic channels lie outside the lumen of the pelvis and have to travel up to the cortico-medullary junction before they can enter into the renal parenchyma.

Renal Vasculature

At the cortico-medullary junction, the branches of the renal artery divide and lie in the long axis of the kidney These branches are known as the arcuate arteries and contrary to original descriptions, they are only linked together by capillary connections (Fig 5). The

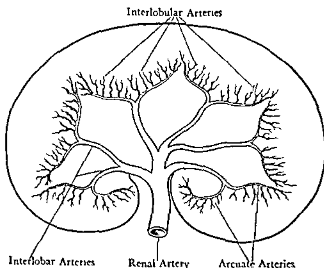


FIG 5 Main branches of the renal arterial tree illustrating that the arcuate arteries are only connected by a capillary anastamosis

interlobular arteries branch off at right angles to these arcades, and penetrate straight into the cortex, where they give rise to short afferent glomerular arterioles, so that even the most distal glomerulus receives its afferent arteriole direct from a relatively large artery. Beyond the glomerulus the blood flows into the efferent arteriole and then into a capacious intercommunicating plexus of capillaries situated between

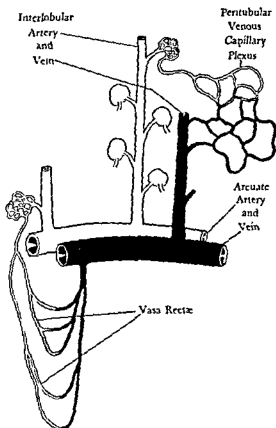


Fig. 6 Schema illustrating the renal circulation of the cortex and medulla.

the tubules (the peritubular venous capillaries) which empties into the interlobular veins (Fig 6).

The blood supply to the medulla passes through those glomeruli which are nearest to the medulla ; these are sometimes known as juxta-medullary glomeruli Anatomically they are distinguished by large arterioles, and it is probable that they can accommodate relatively large blood flows. Subsequently the blood travels down long, looped venous capillaries which penetrate towards the apex of the pyramids

and double back to the cortico-medullary junction to empty into the arcuate veins.

The striking differences between the blood vessels of the cortex and medulla therefore are: (*a*) that the medulla has no direct arterial supply and (*b*) that whereas the peritubular venous capillaries in the cortex form one vast network, the peritubular venous capillaries in the medulla are individual parallel channels with little or no intercommunication

The Interstitial Space

The cortex is almost free of connective tissue and in an ordinary histological preparation the peritubular venous capillaries and the tubules are contiguous, which suggests that there is no interstitial space. It is by no means certain however that this is true in life Electron microscopy has revealed that there are apertures about 0·05 μ wide in the cytoplasm of the endothelial cells which line the peritubular venous capillaries; and that on the outer surface of this perforated cytoplasm there lies an extremely thin basement membrane. The porosity of this membrane is not known, but it may be considerable. Sections from kidneys which have been frozen instantaneously, after being excised from living animals, show that there exists a clear area around each tubule, between the tubule and the peritubular capillary. It is also well established that the blood that drains from a kidney which has just been excised from a living animal has a much lower hæmatocrit than the hæmatocrit of that animal's arterial or venous blood It is probable that the extra plasma lies in the clear areas around the tubules Usually these spaces are not visible, for the plasma they contain escapes with the blood in the capillaries via the cut renal artery and vein

The presence of an interstitial space in the medulla is certain, for the many parallel tubes that it contains are separated by a lagging of connective tissue which is particularly thick towards the apex of the pyramids.

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2

TESTS OF RENAL STRUCTURAL INTEGRITY

THE following methods are used to obtain information about the structure of the kidney :

Clinical Examination of the Abdomen.
Straight X-ray of the Abdomen
Intravenous Pyelography.
Retrograde Pyelography.
Renal Arteriogram
Renal Biopsy.

Clinical Examination of the Abdomen

Obviously this is most helpful in thin patients and may give information about the presence of a tumour, hydronephrosis and polycystic kidneys ; if the kidneys are easily palpable it is usually easy to decide whether or not they are much larger than normal. To obtain the best results from this examination it is essential that the patient move his diaphragm well down with each inspiration, while relaxing the anterior abdominal muscles Some patients seem unable to do this, but may be taught to do so by being told to place their hands palm downwards on the surface of their abdomen while they practice Tenderness in the renal angle or over the kidney anteriorly indicates that there is inflammation which may be due either to infection, infarction or an allergic reaction

A distended bladder is often an invaluable clue to the presence and cause of renal failure.

Straight X-ray of the Abdomen

Such an X-ray is less revealing than an intravenous pyelogram, but it has certain advantages It can be performed at short notice and it is painless. Often the outline of the kidneys may be distinguished so that their size, shape and position can be determined, and it may also be possible to decide whether there are any shadows consistent with the presence of calculi or renal calcification.

Intravenous Pyelography (I.V.P.)

This is achieved by the intravenous administration of sodium diatrizoate (Hypaque) or sodium acetrizoate (Diaginol) at a time when the rate of flow of the urine is minimal. These two substances consist of large molecules containing three radio-opaque iodine atoms, and although they are filtered at the glomerulus the amount filtered is greatly exceeded by the amount that is actively secreted by the proximal tubule cells into the tubular fluid. If large quantities reach the kidney therefore, the tubular fluid and the urine contain high concentrations of radio-opaque material ; radiologically the kidney's parenchyma becomes faintly visible while the calyces and pelves are densely shadowed.

Intestinal gas and movements, fæces and fat may considerably obscure and confuse the results. An aperient should be taken the preceding evening and, if it has failed to act, a small enema should be given It is best to allow the patient to be up and about for 24 hours before the examination, and a low-residue diet and no medicine containing bismuth or similar radio-opaque substances should be taken for at least two days previously. Intestinal gas can sometimes be dispelled by an injection of aqueous pitressin or neostigmine methylsulphate.

The density of the pelvic shadow is dependent upon the following :

(i) The anterior-posterior depth of the iodine-containing urine which the X-rays have to penetrate.

(ii) The rate of urine flow, or in other words, the volume of urine into which the iodine is excreted.

(iii) The rate at which the kidneys can secrete the iodine, which in turn depends on the secretory capacity of the tubule cells and their total number.

To increase the amount and depth of the urine in the pelves and ureters they are forcibly distended by partially obstructing the lower ureters by compression of the lower abdomen with an inflatable rubber balloon. This is best done about 5–10 minutes after the injection of the contrast solution, when its concentration in the pelves has reached a plateau. The rate of urine flow is reduced as much as possible by fluid deprivation or the administration of pitressin tannate in oil. Nothing can be done to increase the rate at which the tubules secrete contrast medium beyond making sure that this is occurring at the tubules' maximum capacity, i e. that the amount of contrast medium presented to the kidney per minute greatly exceeds its capacity to transfer it from the blood into the tubular lumen. In many ways the technique is comparable to that used when estimating a Tm (p 58)

and the intravenous administration of 40 ml of 45 per cent. sodium diatrizoate, or 20 ml of 50 per cent. sodium acetrizoate satisfy these conditions; larger injections only increase the amount filtered and this is a relatively small and insignificant addition

The main value of an I.V.P. is the evidence it gives of the size and configuration of the pelves and calyces; it is also helpful in determining the size, shape and position of the kidneys; and it is sometimes useful in first suggesting that there may be unilateral parenchymal disease Occasionally distortion of a calyx is best seen on a lateral or oblique view.

Though the excretion of the contrast medium in easily visible radiological concentrations gives a relatively good indication that renal function is not grossly impaired, it is important to note that a poor or absent I.V.P. shadow does not necessarily indicate abnormal renal function.

Frequently I.V P. reports state that "the kidney's ability to concentrate is normal . . or good" This is a misleading statement for it must be stressed that one cannot determine the kidney's ability to concentrate from an I V.P, for urine concentration is a function of the distal and collecting tubules, while the excretion of molecules containing iodine is a function of the proximal tubules Occasionally a patient is seen with a tubular abnormality who is quite unable to concentrate the urine above S.G. 1 010 but who can still produce a dense I V.P. shadow, for the number and functional efficiency of the proximal tubules are adequate.

Obviously if one kidney is completely destroyed or if the number of nephrons in one or both kidneys is inadequate to excrete the contrast medium at a sufficient rate to produce a visible concentration, a poor or absent shadow is an indication of failing function But absent or faint shadows on one or both sides occur too frequently with normal kidneys to be accepted as anything but a tenuous suggestion of abnormality and if there is no confirmatory evidence of abnormality from other sources, the I.V P. should be repeated. Occasionally there may be no shadow during the first I.V P., yet a normal shadow is seen a few days later during a second. The reason for these transient anomalies is not known, but it is possible that the apprehension and discomfort, which are an unavoidable part of intravenous pyelography, may sometimes be responsible The patient has to remain in one position on a hard X-ray table for a considerable time and for most of this time he has to endure a severe compression of the lower abdomen Much less stress is known to cause a brisk rise in urine-flow from inhibition of pitressin secretion, or an osmotic salt diuresis (p 243).

Renal failure with a raised blood urea is not a contraindication to the performance of an intravenous pyelogram, there is little evidence

that the intravenous injection of these radio-opaque substances impairs renal function. In most cases of renal failure however, an I.V.P. provides little or no useful information.

Retrograde Pyelography

In current practice a radio-opaque substance is introduced directly into the pelvis of the kidney after cystoscopy and ureteric catheterisation. Sodium diatrizoate (25 per cent) or sodium acetrizoate (15 per cent) is injected under considerable pressure to distend the pelvis and ureter; this is done after the patient has recovered from the anæsthetic so as to avoid overdistension.

The information to be derived from a retrograde pyelogram is obviously confined within the borders of the pelvis, calyx and ureter.

Renal Arteriograms

A radio-opaque substance is injected directly into the abdominal aorta at a point just above the origin of the renal arteries; 20–30 ml. of 70 per cent diodone or 30 ml of 50 per cent. sodium acetrizoate are administered via a needle inserted through the skin of the back, or a catheter introduced through a femoral artery; the total volume is administered in four seconds. The fluid travels rapidly into the renal arteries, capillaries and veins. Exposures are made at intervals of a few seconds following the injection at a time when tubular secretion of diodone is relatively insignificant. It is a highly specialised technique which gives good pictures of the renal vascular tree. It reveals the presence of anomalous arteries and is sometimes most useful in defining the existence of localised areas of disease in the renal parenchyma, and distinguishing between tumours and cysts. The tumours being vascular become radio-opaque in contrast to the cysts which do not cast a shadow. One of the advantages of this technique is that it enables information to be obtained about the substance of the kidney when an intravenous pyelogram has failed to produce a shadow Unfortunately it sometimes gives rise to serious complications. The concentrated dye may cause acute tubular or cortical necrosis, and therefore, a pre-existing impairment of renal function is a contra-indication to renal angiography If a needle is used it may cause a periaortic hæmorrhage, or a traumatic dissecting aneurysm which may obstruct the root of a main abdominal artery.

Renal Biopsy

A small fragment of kidney is obtained by means of a biopsy needle introduced through the renal angle The position of the kidney is first determined by a straight X-ray of the abdomen or an I.V.P., and

precautions are taken to ensure that there are no clotting or bleeding abnormalities Any such abnormality is a contraindication to renal biopsy, as is advanced renal failure, tuberculosis of the kidney, renal tumour, recent renal vein thrombosis and the presence of only one kidney Nor is it wise to perform a biopsy in patients suffering from severe hypertension unless the blood pressure can be lowered during and for a few hours after the biopsy

The patient is placed in the prone position with his abdomen upon a small firm pillow, and the surface markings of the twelfth rib, the iliac crest, and the lateral border of the erector spinæ are indicated with a coloured ink or scratched upon the skin , this is usually done on the right side because of that kidney's greater accessibility. A thin exploratory needle is then used to give the local anæsthetic and to find the position of the kidney The patient is instructed to hold his breath as the needle is inserted , and upon being allowed to continue breathing the needle is left free. When it is in the kidney that part of the needle which is still visible will swing through a considerable arc with each respiration. This phenomenon is an almost certain indication that the needle is in the kidney, but in the obese or oedematous it is sometimes misleading, for the same response may occur when the needle is in perinephric fat , it must be remembered that the needle will also swing if it is in the liver

A renal biopsy (needle or laporotomy) is clearly the only method of making an exact histological diagnosis during life The information which has been obtained in this way has been of the greatest value in throwing light upon the natural course of renal disease It is true that often such diagnostic precision is of no therapeutic benefit to the patient, and that the histological appearance may frequently be surmised from the history, clinical details and past experience of autopsy material ; nevertheless, even in the present era of therapeutic helplessness in regard to most renal diseases there are occasions when an exact histological diagnosis may be of importance in deciding the patient's future treatment For instance, in a patient suffering from proteinuria with mild renal failure and active pulmonary tuberculosis, it may be imperative to decide whether or not the renal lesion is due to the deposition of amyloid material. If it is, clearly every effort, including surgery, should be made to eradicate the tuberculous disease, whereas if the renal lesion is one of chronic glomerular nephritis, less drastic measures may be justifiable. Some-

and hæmaturia with clot colic. The former resolves rapidly and both occur relatively rarely, though microscopic hæmaturia always occurs. Some authorities quote having performed several hundred renal biopsies without any complications while others appear to have had 1–2 per cent. of their cases develop hæmaturia of sufficient severity to produce colic. Renal biopsy, like liver biopsy, is a technique which should not be undertaken lightly and whose contraindications should be carefully noted.

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3

INTRODUCTION TO RENAL FUNCTION AND SOME THEORETICAL CONSIDERATIONS CONCERNED IN TESTING ITS INTEGRITY

THE function of the kidney is to keep the volume and composition of the extracellular fluid within normal limits ; it is also concerned with the maintenance of a normal blood pressure

The composition and volume of the extracellular fluid is controlled by glomerular filtration, and tubular reabsorption or secretion In a day approximately 180 l. of almost protein-free fluid is filtered through the glomerular capillaries into the glomerular space, from whence it passes into the tubule As this filtrate travels down the tubule various substances are either subtracted or added to it, so that eventually only about one litre emerges as urine , this is the water and solutes which the body needs to discard The renal mechanisms involved in regulating the blood pressure are obscure , they are discussed in Section 9 (p. 77).

In normal circumstances every glomerulus is continuously being perfused with blood , there is no evidence that the intermittency of glomerular circulation described in the frog is present in man The rate of blood flow is adjusted by alterations in the afferent and efferent glomerular arterioles Such changes must influence the glomerular capillary pressure and in turn the rate of glomerular filtration Alterations in glomerular filtration rate are, within wide limits, affected by changing the rate of filtration in each glomerulus. There is no evidence that new nephrons are opened up when glomerular filtration rate increases and complete closure of some glomeruli only occurs when glomerular filtration rate is suddenly reduced below 50 per cent.

Normally approximately 120 ml of filtrate are separated from the 600 ml of plasma that pass through the kidney each minute. The ratio glomerular filtration rate renal plasma flow is known as the filtration fraction. It can be seen that in health it is about 0 2. In disease it may vary from 0 1 to 0 3, but it is clear that, as might have been expected, the relationship between the rate of renal blood flow and the glomerular filtration rate remains relatively close.

Glomerular filtrate contains all the diffusible ultrafiltrable substances present in plasma and, ignoring a slight difference caused by the plasma

proteins, they are present in the same concentrations. There is also some indirect evidence that the filtrate contains small concentrations of protein, probably less than 30 mg /100 ml. ; though this is a relatively insignificant concentration, it nevertheless amounts to a filtration of about 50 g. of protein in 24 hours

Theoretical Considerations

The contents of the urine are selected from the plasma by a wide variety of mechanisms. It follows that the methods used to measure the efficiency of these mechanisms also vary. For instance, it will be shown in Section 5 that one of the best methods for testing the kidney's ability to control the sodium content of the extracellular fluid is to place the patient on a salt-free diet, and then to observe whether the kidney is able to diminish the excretion of sodium. Such a method is obviously unsuitable for measuring the kidney's ability to control the extracellular fluid concentration of substances which, regardless of intake, are continuously being manufactured by the body, e g urea and creatinine

It has been found empirically that the most convenient gauge of the kidney's ability to control the extracellular fluid concentration of substances such as urea and creatinine is to calculate the quotient

$$\frac{\text{amount excreted in the urine per min.(mg./min.)}}{\text{concentration in the plasma (mg /ml.)}}$$

or $\frac{UV}{P}$ where U = the concentration in the urine (mg /100 ml), V = the urine volume per min. (ml /min), and P = the plasma concentration (mg /100 ml). This quotient can of course be calculated for any substance which is present in the plasma and the urine, but it is of no value if the result is greatly influenced by factors unrelated to renal function (e g. diet). It is useless, for example, to calculate the quotient for sodium for in a normal person it may vary by more than 100 per cent during a single day The quotients for urea and creatinine, however, are relatively constant for their urinary excretion throughout the day is far more uniform.

The quotient $\frac{UV}{P}$ is inevitably expressed as ml./min (i.e. $\frac{\text{mg /min.}}{\text{mg./ml.}}$ = ml /min.) and is conventionally referred to as a "clearance." This curious term derives from an extension of the fact that the result of dividing the amount excreted in the urine by the plasma concentration gives the least volume of plasma which could have contained the amount excreted. It follows that the quotient can therefore be considered as representing the volume of plasma which must be

completely "cleared" to provide the amount appearing in the urine. The concept of a clearance is only a particular way of thinking about the quotient $\frac{UV}{P}$, it is obviously unrelated to what is actually happening in the kidney, for there is no evidence that some of the plasma is stripped of certain of its contents while the remainder emerges unchanged The disadvantages of the word "clearance" are the tortuous explanations and frequent misconceptions to which it gives rise.

Measurement of Glomerular Filtration Rate

The most precise measurement of glomerular filtration rate is obtained with inulin, for after passing freely through the glomerulus it travels down the tubule without any being subtracted or added by the tubule cells. The quantity that is excreted in the urine in one minute is therefore the same as that which is filtered. But it is known from puncture of the glomerular capsule by micropipettes that the capsular fluid (i e the glomerular filtrate) is identical to plasma ultrafiltrate. Therefore the quantity of inulin present in the urine must, as it passes through the glomerulus, be accompanied by a quantity of water sufficient to keep the inulin concentration in the capsular space the same as in the plasma This volume is clearly that of the glomerular filtrate, it is estimated by calculating the least volume of water (i e plasma) that can have contained the amount of inulin excreted in the urine, i e $\frac{UV}{P}$ The inulin clearance is thus a measure of glomerular filtration rate. For instance if the plasma concentration of inulin is 10 mg /100 ml, and 10 mg of inulin is excreted in the urine in one minute, it is clear that if inulin is not reabsorbed or secreted by the tubule cells, 100 ml of water is passing through the glomerular filter in one minute

For similar reasons the creatinine clearance is also used as a measure of glomerular filtration rate, but it is not so exact as inulin for a small quantity of creatinine is secreted into the tubular fluid by the tubules.

Measurement of Renal Plasma and Blood Flow

The renal plasma flow (R P.F) can theoretically be calculated by the Fick principle using any substance excreted in the urine, provided that the renal arterial (RA), and renal venous (RV) plasma concentrations, the urine flow (V), and the urine concentration (U) of that substance are known :

$$\frac{\text{R.P.F.}}{\text{ml /min.}} = \frac{\text{UV (excretion per minute)}}{\text{RA-RV (arterio-venous difference)}}$$

From this the renal blood flow (R.B.F.) can be calculated from the arterial hæmatocrit (Hct) :

$$\text{R.B.F.} = \frac{\text{R.P.F.}}{1 - \frac{\text{Hct}}{100}}$$

It will be seen below that this laborious procedure is seldom necessary, but it can be performed by obtaining samples of arterial blood from the femoral artery, while renal venous blood is obtained via a catheter introduced through an antecubital or femoral vein.

Clearly a substance that is almost completely excreted by the kidney and therefore has a large RA–RV *difference will give more* accurate results than one like sodium which has an insignificant RA–RV difference. An almost ideal substance is para-amino-hippuric *acid (PAH) which is infused intravenously until a steady plasma* concentration is achieved

If the plasma PAH level is less than 5 mg./100 ml about 90 per cent. *of the PAH reaching the kidney is promptly excreted in the urine* (except in cases of advanced renal failure) In general, therefore, it is not necessary to catheterise the renal vein to sample the renal venous blood, for it can be assumed that *RV* is negligible (i.e. *RV* = *0)* or '

$$\text{R P.F.} = \frac{UV}{RA}$$

In other words the clearance of PAH is a measure of renal plasma flow.

Furthermore, since the *peripheral* venous plasma concentration of PAH is almost identical to that in the arterial blood, it is also unnecessary to sample arterial blood, and the whole technique is greatly simplified.

In clinical work PAH clearances are hardly ever estimated There [illegible] the renal blood flow and the simpler to estimate filtration

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4

TESTS OF GLOMERULAR FUNCTIONAL INTEGRITY

IT has been mentioned earlier that approximately 600 ml of plasma pass through the glomeruli per minute from which are filtered about 120 ml of fluid that is almost free of protein and blood cells Glomerular integrity can thus be studied by measuring glomerular filtration rate and by examining the urine for the presence of protein, cells and casts.

Glomerular Filtration Rate

The four methods most widely used to obtain an indication of the glomerular filtration rate are, in descending order of accuracy

1 Inulin clearance
2 Creatinine clearance
3 Urea clearance.
4 Plasma concentrations of creatinine and urea

Inulin Clearance

An inulin clearance is a protracted procedure for it involves either a continuous intravenous infusion of inulin or its deposition as a subcutaneous depot , many blood samples are needed and, as urine is collected at short intervals, relatively large errors due to incomplete bladder emptying may occur which can only be avoided with certainty by catheterisation , finally the estimation of inulin is not particularly easy. For these reasons glomerular filtration rate, except for research purposes, is hardly ever determined by inulin clearance.

Creatinine Clearance

This is by far the most convenient method of obtaining a fairly accurate estimate of glomerular filtration rate. It is a fortuitous but fortunate coincidence that the endogenous creatinine clearance is so nearly the same as the glomerular filtration rate, for the clearance of pure creatinine is in fact slightly greater than that of inulin, indicating that some creatinine is actively secreted by the tubules Creatinine is measured by the intensity of an orange colour produced upon the addition of picric acid, but plasma contains small quantities of other substances (called chromogens) which also give this colour reaction. In normal circumstances, therefore, the apparent plasma creatinine

concentration is greater than the true concentration and this in turn causes the calculated creatinine clearance to be lower than the true clearance (if $C = \frac{UV}{P}$, when P is raised C is reduced) It is this apparent creatinine clearance which is close to that of glomerular filtration. With renal failure however, when glomerular filtration rates are low plasma creatinine rises without a corresponding rise in plasma chromogens, and the estimated plasma creatinine approaches the true value. The estimated or apparent creatinine clearance then also approaches the true clearance, tending to be 10–30 per cent greater than the glomerular filtration rate. This seems a big discrepancy, but as the larger errors occur at the lower rates of glomerular filtration it is not important, for instance a 30 per cent. error when the glomerular filtration rate is 10 ml./min. is not of great moment.

The clearance of creatinine is a much more convenient determination to make than that of inulin, for creatinine is already present in body fluids; its plasma concentration being remarkably steady throughout the 24 hours. Creatinine clearance tests can therefore be performed over long periods without the necessity of continuous intravenous administration; and because the plasma concentration is so constant only one sample of blood need be taken for a 24-hour collection of urine. Such long periods minimise inaccuracies caused by incomplete bladder emptying or slipshod timing of the duration of urine collection; they also diminish the effect of transient emotional reactions on renal function.

Procedure for a 24-hour Creatinine Clearance

The basic requirements are a 24-hour collection of urine and one sample of blood taken at any time during this period. But because an accurately timed collection of urine is so incredibly difficult to obtain, it is perhaps worth while describing some of the difficulties which are encountered. A 24-hour collection of urine can start at any convenient hour, e g 9 a m., at this time the patient is asked to empty his bladder and this urine is discarded; for the next 24 hours all the urine that is passed is collected into one container and the collection ended when the patient is asked to empty his bladder for the last time at about the same hour as on the previous day, this urine being included in the 24-hour collection. It is clearly of no importance if the actual duration of the collection period is a few hours more or less than 24, so long as it is accurately timed. The volume of the urine is then measured and the rate of urine flow per minute is calculated by dividing this volume by the number of minutes which the collection period has lasted. A convenient slogan is that the urine collection should be

"timed to the nearest minute and measured to the nearest ml" A screw-topped bottle full of this urine, and the blood sample, are then sent together to the laboratory for creatinine estimation and calculation of the clearance

This simple manœuvre may be vitiated by the following accidents. (1) Unless the patient has been warned, urine may be passed during defæcation and thrown away; (2) unless urine is placed immediately into a large container it may be lost and not included in the 24-hour collection, (3) occasionally the urine passed at the beginning of the collection period is included in the total collection, (4) it is not unknown for a collection period to be officially noted as having started when the urine bottle was handed to the patient, regardless of the fa that he may have four or five hours' urine in his bladder Many c these troubles can be avoided by making the patient responsible fo his own urine collection.

Urea Clearance

The clearance of urea is the most widely used test of renal function, its value depends on the fact that urea clearance is directly related to the glomerular filtration rate As a guide to the rate of glomerular filtration however, it is inferior to the creatinine clearance. Its main disadvantages are (1) The clearance of urea is considerably less than the rate of glomerular filtration, (2) this discrepancy varies with the rate of urine flow, and (3) the ward procedure involved in a urea clearance makes it very vulnerable to technical inaccuracies.

In normal subjects, when the urine flow is greater than 2 ml/min urea clearance is about three-fifths of the glomerular filtration rate, at lower urine flows it is less This relationship is illustrated in Fig 7 It suggests that though there is every reason to believe that urea is filtered through the glomerulus at the same rate as inulin and creatinine, for urea is a small highly diffusible molecule, a great deal must be reabsorbed as it passes down the tubule. At urine flows above 2 ml/min. the amount reabsorbed is constant and is about two-fifths of the quantity which has been filtered, and as the urine flow becomes less so gradually more urea is reabsorbed In an average man, therefore, the urea clearance at urine flows above 2 ml/min is $3/5 \times 120 =$ 75 ml/min), such a clearance (obtained at urine flows greater than 2 ml./min, is sometimes called the maximum urea clearance For traditional reasons this absolute figure is converted into a percentage, i.e. a urea clearance of 37 ml/min is reported as being $\frac{37}{75} \times 100 =$ 50 per cent. of normal The merit of this system is that one does not have to remember the normal urea clearance, but why this dispensation

to feeble memories should be extended to urea clearance is not certain. It probably dates from the time when clinicians were considered to be unable to grasp absolute figures.

When the urine flow is less than 2 ml./min. urea clearance varies with the rate of urine flow, but in normal subjects, if the clearance is then multiplied by the square root of the rate of urine flow, a figure is obtained which approximates to an average of 54 ml./min., regardless of the rate of urine flow. This mathematical jugglery is called a "standard urea clearance"; it is a manœuvre which adjusts all the true clearances measured at rates of urine flow below 2 ml./min. as if they had all been estimated at a standard urine flow of 1 ml./min. The

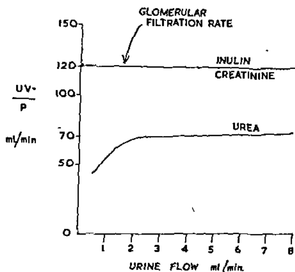


FIG. 7 Schema showing the relationship between the clearances of inulin, creatinine and urea to the urine flow and to each other

results are again expressed as a percentage. This rigmarole has probably caused more confusion about the nature of renal function in those not familiar with the subject than any other of the many mathematical obscurities which so often enshroud the kidney. It is obvious that a "standard urea clearance" is *not* a clearance and that the use of the word "standard" in this context is misleading. For clinical purposes these complications are best avoided by doing urea clearances at rates of urine flow above 2 ml./min.

Procedure for Urea Clearance

Plasma levels of urea may fluctuate, and urea clearances vary with the urine flow, so that clearances have to be performed over short

periods It is customary to perform them in the morning when the patient is in a fasting state. In order to raise the urine flow above 2 ml./min two glasses of water are given about half an hour before the beginning of the first period when the bladder is emptied and the urine discarded An hour later the bladder is emptied again, the urine is saved and a sample of venous blood is taken Finally the urine is collected once more after a further hour. The volume of the two urine collections is measured and a sample of each collection is then sent, together with blood, to the laboratory for urea estimation and calculation of the clearance. The point of having two collection periods is to enable a comparison to be made between these two clearances so that the accuracy of the urine collection may be gauged

Serious errors will occur if the bladder cannot be emptied properly or if those concerned with noting the duration of the urine collection period are horologically amoral Occasionally the test may be influenced by the emotional reactions of the patient to having to empty his bladder at predetermined intervals, or to having to submit to venepuncture.

There is a point in the laboratory technique which sometimes causes confusion. The urea clearance is usually expressed as a "blood" clearance, i e $\frac{UV}{B}$ (as opposed to $\frac{UV}{P}$). This is possible because urea is freely diffusible into red cells, and the concentration of urea in whole blood is almost identical to its concentration in plasma. Blood urea estimations can therefore be performed on spun red cells, leaving the supernatant plasma available for other estimations.

Plasma Concentrations of Urea and Creatinine as a Guide to the Rate of Glomerular Filtration

Normal plasma urea concentrations vary between 15–35 mg per cent, the lower values tending to be found principally in children, and during pregnancy normal plasma creatinine concentrations vary between 0.5–1.2 mg per cent If the clearance of these substances parallels the rate of glomerular filtration it is clear that when the filtration rate falls their plasma concentrations will rise. It would seem simpler therefore, when trying to gauge the state of the glomerular filtration rate, to be guided by an estimation of these plasma concentrations instead of having to perform clearances Unfortunately the relation between glomerular filtration and plasma concentration is such that these concentrations are only of limited usefulness in this respect The reasons for this are given below.

The plasma concentrations of urea and creatinine depend on their

rate of [illegible]

trations to rise until a new equilibrium is reached Conversely if glomerular filtration rate remains constant and the rate of urea or creatinine production increases, their plasma concentrations will also increase. The connection between glomerular filtration, the production of urea and creatinine, and their plasma concentrations are analogous to the situation that obtains when fluid is being poured into a funnel.

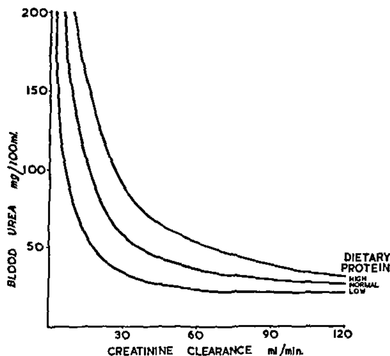


FIG 8 Schema of the relationship between glomerular filtration rate (creatinine clearance) and the blood urea at varying levels of protein intake

[illegible] on the diameter [illegible] above the outlet to force the fluid out as fast as it is being poured in at the top If the outlet is then partially occluded or the rate of delivery into the funnel is increased the level of fluid in the funnel rises higher until a new equilibrium is reached The supply of liquid into the funnel represents the production of urea and creatinine; the height of liquid in the funnel their plasma concentrations; and the diameter

of the outlet the rate of glomerular filtration. When each new equilibrium is reached the rate of elimination equals the rate of production

The relationship between the blood concentration of urea and the glomerular filtration rate is illustrated in Fig. 8 It can be seen that as the glomerular filtration rate diminishes there is at first only a small absolute rise in blood urea so that when the filtration rate is down to half its normal value the blood urea is still only 35–50 mg /100 ml. Further reductions in filtration rate, however, produce large absolute changes

The implications behind this relationship are . (1) Plasma concentrations of urea and creatinine show little absolute change until,

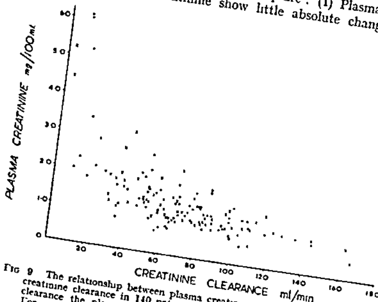


Fig 9 The relationship between plasma creatinine concentration and the creatinine clearance in 140 patients It can be seen that at any one clearance the plasma creatinine concentrations are widely scattered For instance, there are several clearances below 50 ml /min with normal creatinine concentrations (i e below 1 2 mg /100 ml)

functionally, the patient has lost one kidney ; (2) when the glomerular filtration rate is low a small additional reduction in filtration rate will produce large changes in plasma concentrations The latter is particularly striking in a patient with a moderate degree of renal failure and a blood urea of 50–60 mg per cent who develops cardiac failure, or who has a hæmorrhage , the blood urea may then rise to 150–200 mg per cent with a superimposed decrease in glomerular filtration rate of only 10–20 ml /min.

It is clear that if the blood urea concentration is greater than 60 mg per cent., or the plasma creatinine above 2 mg. per cent., there

is probably severe depression of glomerular filtration rate; but values below these are indifferent indications of glomerular function (Fig. 9) This is not only because at these lower concentrations large disturbances of glomerular filtration cause small absolute changes in plasma concentrations, but also because such small changes may be due to other factors than alterations in filtration rate. This is particularly applicable to urea, for (1) its rate of elimination in the urine is not only related to the glomerular filtration rate but also to the urine flow, and (2) its rate

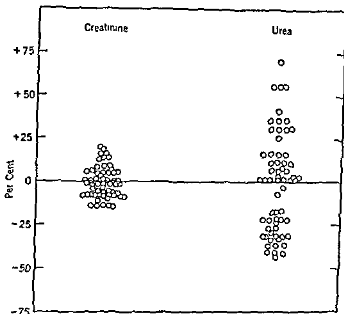


FIG. 10 Serum concentrations of creatinine and urea The percentage [illegible] concentrations of creatinine and urea [illegible] r kg body [illegible] vary less [illegible] Macmillan, New York)

of production is profoundly affected by dietary protein content and endogenous protein catabolism Fig. 8 illustrates the effect of high and low protein diets on the relation between blood urea and glomerular filtration rate It shows that with low protein intakes the level of blood urea may remain within the normal range though there is a substantial fall in glomerular filtration rate (the impaired production of urea in liver disease may also cause a similar effect). Conversely, a high protein diet (Fig. 10), or an increased protein breakdown (Fig. 11), will raise the blood urea to pathological levels though the glomerular filtration rate is normal or unchanged These factors also influence the

plasma concentrations of creatinine but to a much smaller extent (Fig 10)

Finally, plasma concentrations of both urea and creatinine are often misleading because they lag behind changes in glomerular filtration rate. This is most obvious during the first few days of acute renal failure when there may be a gross reduction in glomerular filtration rate with initially a relatively small rise in blood urea or creatinine.

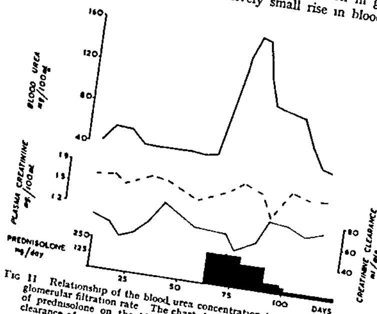


FIG 11 Relationship of the blood urea concentration to other factors than glomerular filtration rate The chart shows the effect of large quantities of prednisolone on the blood urea, plasma creatinine and creatinine clearance of a patient with a nephrotic syndrome and some impairment of creatinine clearance There occurred a precipitous rise in blood urea and a minimal change in plasma creatinine, simultaneously there was a slight fall in creatinine clearance but to a level which seven weeks earlier had only been accompanied by a minor rise in blood urea

Conclusion

In a patient in whom renal disease is suspected the finding of a substantial rise in blood urea or creatinine is nearly always good evidence of a severe reduction in glomerular filtration rate. If the patient has been on a low protein diet however, an estimation of the plasma concentration of urea may be grossly misleading (e g. blood urea of 70 mg per cent. with a glomerular filtration rate of 10 ml /min); in these circumstances the creatinine concentration permits a much more accurate assessment of the filtration rate With plasma concentrations in or near the normal range it is necessary to estimate a

24-hour creatinine clearance or a one-hour urea clearance before it can be decided whether there is any impairment of filtration rate.

Proteinuria

It is probable that glomerular filtrate contains 10–20 mg per cent. of protein, and that the relative lack of protein in the urine is due to its being reabsorbed by the tubules. The normal 24-hour protein excretion is 0–90 mg In theory, therefore, the presence of protein in the urine means either that an increased amount has escaped from the glomeruli or that less has been reabsorbed by the tubules But there is evidence that though diminished tubular reabsorption may occur, proteinuria is usually due to changes in the glomeruli.

Proteinuria is usually detected by precipitation by boiling, or by the addition of salicyl sulphonic acid. The normal low protein concentration of the urine is not apparent with these tests; otherwise they are relatively delicate and with 25 per cent. salicyl sulphonic acid a protein concentration of 0·2 g /l is evident as a "trace," and a 5 0 g /l will give a heavy flocculent precipitate. For clinical purposes it is traditional to comment on the proteinuria in a semiquantitative manner, a barely perceptible precipitate being called a "trace" and a heavy precipitate ++++, with + to +++ in between. This is more useful if the concentration (i e specific gravity) of the urine is measured at the same time, for the rate of protein excretion is relatively constant throughout the 24 hours and is related to the glomerular filtration rate, whereas the concentration of protein fluctuates with urine flow. In other words, the finding of + of protein in a dilute urine indicates a much greater rate of protein loss than a similar finding in a concentrated urine. An estimate of the rate of protein excretion is conveniently obtained by measuring the protein concentration of a 24-hour volume and multiplying this figure by the urine volume. For daily routine clinical use it is convenient to measure the protein concentration with Esbach's technique; the urine is placed in a graduated test-tube and the protein is precipitated with picric acid, the height of the precipitate after standing for 24 hours gives an indication of the protein concentration.

In general one may say that proteinuria does not occur with disease of the lower urinary tract; with severe exudative or hæmorrhagic lesions there may be a trace of protein, but this will only occur when the pus and blood are visible macroscopically. It is essential to realise that it is the presence of protein in the urine which is the important abnormality; and that the rate of protein excretion is of secondary importance as advanced renal failure may be associated with only a

trace of protein in the urine. Proteinuria is almost always present when there is disease of the renal parenchyma, and though there are many transient and unimportant causes of proteinuria, it should not be dismissed, particularly if it is persistent In women a trace of protein may be caused by contamination with vaginal discharge ; the distinction is made by testing a sample of urine obtained with a catheter

An electrophoretic separation of urinary proteins distinguishes the proteins being excreted They are the same as those present in the plasma, although their relative concentrations are different, for their rate of urinary excretion seems to be related to molecular size. The loss, therefore, of albumin and α_1 globulin is usually much greater than that of α_2 globulin, a distribution which is characteristic in the nephrotic syndrome Occasionally the pattern may be different , in acute nephritis the urinary proteins are in the same proportions as those in the plasma, while in myelomatosis a small globulin may appear without albuminuria.

Urinary Deposit

Red and white cells and hyaline casts are found in normal urine. In a freshly passed urine of moderate concentration, 10 ml of which has been spun for 10 minutes and the deposit examined microscopically with 1/6 objective, the normal rate of excretion of these constituents will appear as an occasional unit in the microscopical field Any greater frequency is suspicious and it is definitely abnormal for there to be several red or white cells per field Unfortunately this simple method of gauging the rate of cell excretion is most inaccurate. It is useful as a routine laboratory procedure but if a precise estimate of the rate of cellular excretion is required it is necessary to collect a timed sample of urine and to count the cells in a counting chamber. Addis originally established this technique using 24-hour urine collections. Later he used shorter collection periods, for, upon standing, the cells in the urine are apt to lyse and disappear Houghton and Pears have recently devised a modification which is described in detail below ; it is convenient, accurate and simple.

The subject empties his bladder as completely as possible, the time is carefully noted, and the urine discarded Three to four hours later, the bladder is emptied once more, the time again noted and the urine kept. In female patients who have a vaginal discharge it is best to collect the urine with a catheter , male patients should avoid preputial contamination Within two hours the specimen is thoroughly shaken, precipitated phosphates dissolved by adding a few drops of glacial acetic acid, and 10 ml. is measured into a graduated centrifuge tube. After spinning at 2,000 r.p.m for five minutes, 9 ml. of the supernatant

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is discarded and the remaining 1 ml. thoroughly mixed with a Pasteur pipette. The cells in a drop of this fluid are then counted in 2 c.mm. of the ruled area of a Fuchs-Rosenthal counting chamber under 1/6 objective. Disrupted and degenerated cells are not included. The results are calculated as follows, and expressed either as the number of red cells or the number of leucocytes and non-squamous epithelial cells excreted per hour.

$$N = \frac{500 \times C \times V}{10\,T} = \frac{50\,CV}{T},$$

where C = actual number of cells counted, V = volume of specimen in millilitres, T = time in hours over which the specimen was formed, and 500 = the factor to convert 2 c.mm. to 1 ml. The cells are more easily recognised if the urine is not too concentrated; it is useful therefore, to see that the patient passes about 200–400 ml. of urine in the three to four hours of the collection period.

With this technique an excretion of red cells greater than 200,000 per hour is abnormal; the average normal excretion is about 50,000 per hour with a range of 0 to 200,000. The rate of excretion of the white and squamous cells combined is approximately the same.

It is important to note that there is a misleading relationship between the colour of the urine and the concentration of red cells it contains. For instance, frank hæmaturia, i.e. the macroscopic appearance of red cells in the urine sufficient to cause an acid urine to be brown or an alkaline urine to be red, is produced by only 0.2 ml. of blood in 500 ml. of urine.

Many different types of casts may be seen—blood, granular, hyaline, waxy and broad—the most important diagnostically being granular and blood casts. All are basically composed of a mixture of precipitated protein and a polysaccharide into which are imbedded the red cells which are leaking through the diseased glomeruli, or the degenerated tubule cells which are flaking off the walls of the nephron. Hyaline casts are transparent, without any cells attached to their surfaces; they are of no importance clinically. Blood casts are characterised by a diffuse orange-yellow colour which is the hæmoglobin from hæmolysed red cells; these casts tend to break into short stumpy rectangular masses which are easily overlooked. Granular casts contain either relatively intact red cells or desquamated tubular cells. The highly significant fact about blood and red cell granular casts is their indication, beyond any shadow of doubt, that the hæmoglobin and red cells they contain must have originated from the renal parenchyma and not from the lower urinary tract.

Accordingly, there flows into the distal tubule approximately 25 ml./min of an isotonic fluid containing large amounts of sodium, chloride, and waste products, with a *p*H which is the same as that of plasma The principal functions of the distal tubule are to adjust the *p*H, osmolarity and electrolyte content of this fluid and *to prevent the reabsorption of the waste products.*

The following tubular functions will be discussed ·

1. Water excretion.
   (*a*) Urine concentration.
   (*b*) Urine dilution and water elimination
2. Control of acid base balance and urine acidity
   (*a*) Hydrogen ion excretion.
   (*b*) Ammonia excretion.
3 Sodium excretion.
4. Potassium excretion.
5. Calcium excretion
6 Phosphate excretion.
7. Amino-acid excretion.
8 Maximal tubular capacity to reabsorb glucose and secrete PAH

WATER EXCRETION

The kidney's ability to modify the rate of urine flow is largely responsible for the constancy of the volume and the osmolarity of body fluids. The rate of urine flow is itself mainly determined by the tubule's ability to control the concentration of the tubular fluid as it passes through the distal and collecting tubules In the following account the terms *hypotonic*, *isotonic*, and *hypertonic* refer respectively to osmolarities which are less than, equal to, and greater than those of plasma Osmolarity can be defined as the concentration of particles in a solution

As the isotonic tubular fluid passes through the first part of the distal tubule it becomes *hypotonic*, owing to a proportionately greater reabsorption of electrolytes than water. This has been demonstrated directly in animals by tubule puncture (Fig. 13) ; in man indirect experiments suggest a similar mechanism is present It seems that the fluid in the first part of the distal tubule is always hypotonic whether the final urine is hyper- or hypotonic.

The hypotonic tubular fluid from the first part of the distal tubule either remains hypotonic as it travels down the second part of the distal and collecting tubule and hypotonic urine is excreted ; or it becomes isotonic in the second part of the distal tubule, hypertonic in the collecting tubule (Fig. 13) and hypertonic urine is excreted.

5

TUBULAR FUNCTION AND TESTS OF TUBULAR FUNCTIONAL INTEGRITY

THE functions of the tubule are to reabsorb, or prevent the reabsorption of the contents of the tubular fluid, *and to secrete into the tubular* lumen substances which are either circulating in the peritubular venous capillaries or which are formed by the tubule cell. These processes are under the control of a wide variety of hormones, plasma electrolyte concentrations and gas pressures

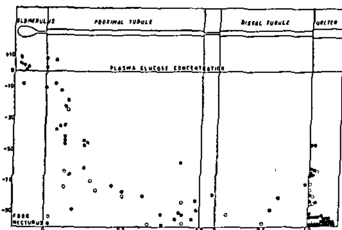


FIG [illegible] differences in glucose [illegible] *J Physiol* [illegible]

It has been shown that the principal function of *the proximal* tubule is to reabsorb about 80 per cent. of the total solids and water from the glomerular filtrate in such a way that the osmolarity and *p*H *of the fluid remaining in the tubular lumen* are identical with those of plasma. The solids are reabsorbed in unequal proportions so *that* while proteins and glucose, for instance, appear to be almost completely reabsorbed (Fig. 12), sodium chloride is only partly reabsorbed, and there is little or no reabsorption of urea and creatinine.

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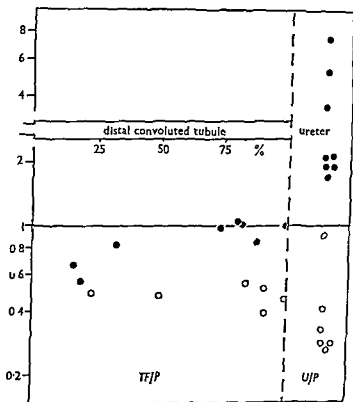
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These dispositions probably explain why in disease, the ability to excrete a hypotonic urine may persist after the ability to make the urine hypertonic has disappeared. It is evident that the urine is made hypotonic or hypertonic at different sites; it is therefore possible that one site may be more diseased than the other.



FIG

The final volume and concentration of the urine is largely controlled by the level of circulating antidiuretic hormone (ADH). When the plasma ADH concentration is low, following a drink of water or disease of the neurohypophysis, the urine is hypotonic and is excreted in large volumes; when the ADH concentration is raised following dehydration

the urine is hypertonic and only small amounts are excreted. It is probable that the cells upon which ADH acts are those of the second part of the distal tubule and the collecting tubule (see above). Some of the other factors which are concerned in concentrating the urine are mentioned below.

Occasionally the misconception that changes in urine flow reflect changes in renal blood flow is encountered. It is perhaps necessary to stress therefore, that no such relationship exists except in the most extreme conditions of renal ischæmia, and then only if the renal blood flow has been rapidly reduced or has almost ceased.

The highest urine concentration attainable is about 1,300 m osmole l. (S G 1 040) which is about four times greater than the concentration of plasma (approximately 300 m.osmole l or S G. 1 010) while the lowest concentration is about 50 m osmole l (S G 1·001)

Methods Used to Measure the Concentration of the Urine

It is customary to measure the concentration of the urine by its specific gravity, which is an indication of the weight of the solutes in solution The kidney's capacity to concentrate however, is related to the concentration of particles in solution (i e the osmolarity) and not to their weight This fact is most easily demonstrated by measuring the specific gravity of urine following an intravenous pyelogram when values of S G 1·060 may be found Such values are much greater than any obtained following dehydration and are due to the excretion of large heavy molecules of radio-opaque substance, the particle concentration of such urine is within normal limits.

The concentration of particles per unit volume (i.e. the osmolarity of a solution) may be calculated from a determination of its freezing point or vapour pressure These techniques are laboratory procedures, and it is fortunate that when urine contains only normal constituents, the correlation between specific gravity and osmolarity is sufficiently close for specific gravity to be used as a clinical guide to the osmolarity of the urine This relationship is illustrated in Fig 14, which also shows that if urine contains much glucose the specific gravity will be greater at a fixed osmolarity, than in normal urine, and, conversely, if the urine contains much urea (a less dense molecule) the specific gravity will be lower

Clinical hydrometers are convenient but relatively coarse instruments with which to measure specific gravity, it is important therefore that they should be used with care. In order to check incorrect graduations clinical hydrometers should always be tested in water each time they are used, and, to avoid surface tension errors on the stem, the hydrometer should be spun and plunged well into the urine

Detergents should not be used for cleaning urine bottles or specimen glasses, for these lower surface tension and increase the measured specific gravity. And the specific gravity should never be measured in freshly passed warm urine, for hydrometers are standardised at a temperature of 16° C.; for every 3° C. above this temperature the specific gravity will appear to be 0·001 less than its true value, i.e. if a

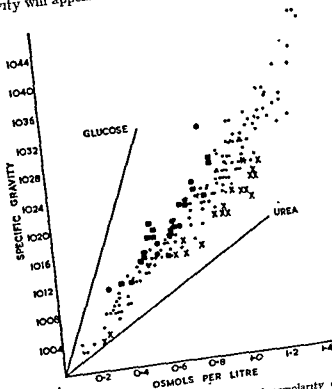


FIG. 14 Relationship between specific gravity and osmolarity of urine. Different urines are shown as follows with no sugar or protein (.), with +++ sugar (●), with +++ protein (■), after 25 g urea by mouth X). Lines are also given showing the relationship between specific gravity and osmolarity of glucose and urea solutions. (Miles and de Wardener, 1954, *Brit med J*)

hydrometer is placed in urine at 37° C. and shows a reading of 1·013, the true specific gravity is 1 020 An adjustment is also necessary when there is gross proteinuria; 0·001 is subtracted for every 5 g./l. of protein

(Certain hydrometers have some remarkable interpretations on the opposite side to the specific gravity numbers. From S.G. 1·016 to 1·020 there is the letter N which indicates the "Normal range," from

S G. 1·020 to 1·026 there is the letter S for Sugar, and from S G. 1·026 to 1·044 there is the word DIABETES written in large capitals. Fortunately these misleading obscurities are rarely noticed.)

Procedure Used to Test the Tubule's Ability to Concentrate Urine

This test can be performed by depriving the patient of fluid or by using an injection of pitressin tannate in oil. Before doing either,

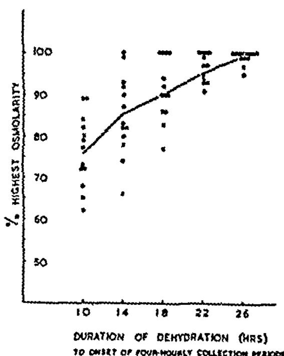


FIG [illegible]

the specific gravity of a sample of urine passed on waking should be measured, for if such a random sample is greater than 1·018 [illegible]

osmolarity and a shrinkage of the extracellular volume, both changes which are known to increase antidiuretic hormone production. The

urine becomes concentrated but often does not approach its maximal value for 24–36 hours (Fig 15) This is rather a long time to dehydrate patients and a convenient clinical compromise is to do the test over a period of 24 hours as follows The period starts at midday when the intake of all fluid, including ice creams, soups and fruit ceases until midday of the following day. The concentration of all urine samples passed between waking and midday of the second day is estimated, and one of these should equal or be greater than S.G. 1·022. The normal range of urine concentration obtained with this procedure varies from S G. 1·022 to S G. 1 040 The highest figures are rarely seen in persons over the age of 20. Occasionally an apparent inability to concentrate

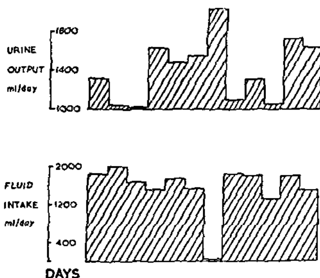


Fig 16 The effect of a day's fluid deprivation on an anxious subject More urine was passed on the day during which she was deprived of fluid than on any other day

is due to the test being performed during a diuresis caused by the spontaneous (and sometimes induced) excretion of oedema fluid.

Fluid deprivation is nearly always unpleasant for the patient, and occasionally, if a severe negative fluid balance develops because of an inability to concentrate, the test may even be dangerous The test should always be terminated if the loss of body weight exceeds 4 per cent. For these reasons the test is hardly ever repeated, which greatly lowers its value. The test may also be vitiated by the patient's emotional reactions to having his " kidneys tested " and being deprived of fluid (Fig. 16).

Pitressin Tannate in Oil. Fluid deprivation and its discomforts and disadvantages can be avoided by giving instead an injection of pitressin tannate in oil Theoretically one might expect the concentration of the urine to be the same whichever method were used In practice the concentration following pitressin is slightly less than after fluid deprivation ; but for clinical purposes this is not important, as the discrepancy between the two techniques gradually becomes smaller as the ability to concentrate diminishes (Fig. 17)

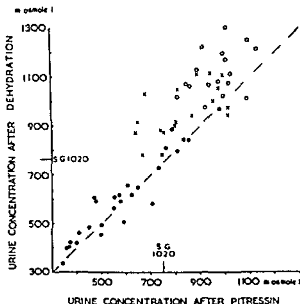


Fig 17 [illegible]

The test is performed by giving an injection of 5 units of pitressin tannate in oil subcutaneously some time before breakfast and measuring the concentration of all urine samples passed during the next 24 hours During this time the patient may eat and drink what he wishes , it is only necessary to make sure that he has not recently been advised to drink larger quantities than his natural inclinations require. If large amounts of water are inadvertently taken the only abnormal symptoms will be a feeling of torpor and a headache.

With this method the highest specific gravity obtained should be 1·020 or above. The effect of pitressin tannate in oil only lasts about 24–48 hours so that the test can be repeated at fairly frequent intervals, both to confirm earlier results and to follow the course of a disease. Intervals of one week between tests have been found satisfactory.

The use of pitressin tannate in oil has one serious disadvantage. The pitressin tannate is mixed with oil and after prolonged standing it settles at the bottom of the ampoule where it looks like an insignificant brown discoloration and is easily overlooked. To avoid its being left behind those actually giving the injection should be aware of this fact, and that it is thus often necessary to warm and shake the ampoule vigorously before use, and occasionally to scrape the solid with the point of a needle. The transfer of the oil and pitressin from the ampoule to the syringe is also made easier by using a large-bore needle.

Interpretation of the Urine Concentration Test

In order to understand the result of a concentration test it is necessary to keep in mind the three factors which are directly concerned in concentrating the urine ; they are :

1. The concentration of circulating antidiuretic hormone (ADH).
2. The ability of the tubules to respond to the antidiuretic hormone.
3. The rate of solute output.

The concentration of circulating ADH is regulated by both the amount of ADH produced by the neurohypophysis and the rate at which it is being destroyed at the periphery, particularly in the liver and kidney. As yet there is no evidence of any pathological condition in which there is an abnormal rate of ADH destruction ; changes in the circulating level of ADH are therefore due to alterations in its production by the neurohypophysis A wide variety of factors influence neurohypophyseal function including the osmolarity of the extra- [illegible] involving [illegible] ed because [illegible] atter may be reversible. The acquired disturbances which may be reversible initially include fever, urinary tract obstruction (*hydronephrosis*) (Fig. 18), potassium deficiency, hypercalcuria, water intoxication, hypo-adrenalism and occasionally certain acute phases of some generalised allergic diseases. In many of these conditions the urine may be persistently hypotonic even during dehydration or the intravenous administration of pitressin ; this is particularly characteristic

[illegible]

able time so that the level of circulating ADH, and the concentration of the urine are high, and if at this time some substance is then administered which is promptly excreted by the kidney, there is not only a prompt increase in solute output, but also a rise in urine flow and *a decrease in urine concentration* This phenomenon is called an osmotic diuresis and is illustrated by the curve A in Fig. 19 It can be

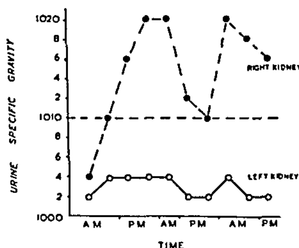


FIG 18 The effect of a raised intrapelvic pressure on the ability to concentrate The observations were made on a patient with a left-sided [illegible]

seen that in these conditions of maximal ADH activity an osmotic diuresis is associated with a fall in urine concentration towards that of plasma, but that the urine concentration remains greater than plasma

If on another occasion an osmotic diuresis is induced when the level of circulating ADH is less than during the experiment just described, [illegible]

when there is no ADH in the circulation, an osmotic diuresis increases

With this method the highest specific gravity obtained should be 1·020 or above. The effect of pitressin tannate in oil only lasts about 24–48 hours so that the test can be repeated at fairly frequent intervals, both to confirm earlier results and to follow the course of a disease. Intervals of one week between tests have been found satisfactory.

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The ability of the tubules to respond to ADH may be impaired because of a permanent congenital defect or an acquired lesion ; the latter may be reversible. The acquired disturbances which may be reversible initially include fever, urinary tract obstruction (hydronephrosis) (Fig. 18), potassium deficiency, hypercalcuria, water intoxication, hypo-adrenalism and occasionally certain acute phases of some generalised allergic diseases. In many of these conditions the urine may be persistently hypotonic even during dehydration or the intravenous administration of pitressin ; this is particularly characteristic

able time so that the level of circulating ADH, and the concentration of the urine are high, and if at this time some substance is then administered which is promptly excreted by the kidney, there is not only a prompt increase in solute output, but also a rise in urine flow and *a decrease in urine concentration.* This phenomenon is called an osmotic diuresis and is illustrated by the curve A in Fig 19. It can be

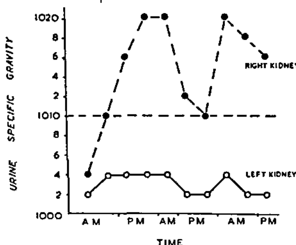


Fig 19 The effect of a [illegible]

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by excising one kidney completely and about 50 per cent of the other Though the remaining piece of kidney contains presumably normal nephrons such an animal is unable to produce concentrated urine. It is likely that similar conditions exist in many forms of renal disease associated with much parenchymatous destruction If the patient is eating normally the total solute excretion rate must remain relatively unchanged, yet these solutes are being excreted through a considerably reduced number of nephrons In such circumstances a diminished capacity to concentrate is probably due in part to the osmotic diuresis *per nephron* which must be taking place, rather than any particular inability of the tubules to respond to circulating ADH.

It is more difficult to understand the failing kidney's inability to produce a dilute urine, for the analogy of the osmotic diuresis is not applicable It is true that in many patients the ability to dilute the [illegible] as that of plasma and it must be presumed that at this stage there is a true failure of tubular cells as well as an osmotic diuresis.

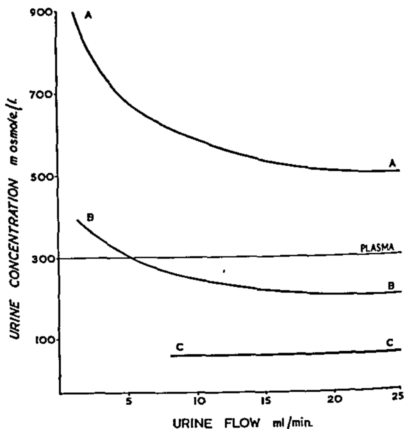
Procedure to Test the Tubule's Ability to Produce a Dilute Urine and Eliminate a Water Load

The test is started early in the morning and is performed in the fasting state After emptying the bladder the patient is asked to drink one litre of water in about 10–20 minutes It is inadvisable to ask the patient to drink this amount more rapidly, for in some cases this will only induce nausea and vomiting with the release of large quantities of ADH , it is also advisable to sweeten the water with fruit juice Urine is collected at hourly intervals for four hours and the concentration of each specimen and the cumulative total are measured During these four hours a normal person should excrete 800 ml or more, and the concentration of at least one specimen should be below S G 1 004

Apart from the risks of nausea and vomiting, this test is subject to other causes of inaccuracy For instance, smoking may inhibit a water diuresis , or emotional reactions may cause either (1) an exuberantly high rate of urine flow unrelated to the patient's normal response to a water load or (2) an almost complete [illegible] expe [illegible] I [illegible] to excrete a water load can be caused by hypoadrenalism, or a defect in water absorption from the bowel

the urine flow but there is little or no associated change in the urine concentration, for it is already at its lowest (line C).

The explanation of these curves is problematical, but it is clear that to obtain all three from one subject the tubules must be capable of manufacturing both hypotonic and hypertonic urine. It is also evident



FIG

that a high solute excretion rate is not compatible with a high urine concentration however great the level of circulating ADH.

If the total solute output remains unchanged but the number of nephrons is reduced, the solute excretion rate for the remaining nephrons is increased and an osmotic diuresis occurs in each nephron. This is the situation that can be produced experimentally in animals

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In addition to renal disease a persistent impairment in the ability to excrete a water load can be caused by hypoadrenalism, or a defect in water absorption from the bowel

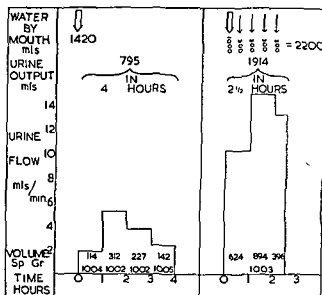


FIG [illegible]

CONTROL OF ACID-BASE BALANCE AND URINE ACIDITY

Plasma hydrogen-ion concentration is maintained close to *p*H 7 4 by a variety of mechanisms ; the most important being the control of the $B.HCO_3/H.HCO_3$ buffer system (where B = metallic cations, i.e. sodium, potassium and calcium). In this system the level of carbonic acid is regulated by the excretion of CO_2 by the lungs, and the concentration of bicarbonate (mainly in the form of sodium bicarbonate) by the kidney's ability to excrete an acid or alkaline urine.

On a normal diet the *p*H of the blood can only remain constant if either pulmonary ventilation rises above normal, or if about 40–60 mEq of hydrogen ions are excreted in the urine each day. This represents the nett load which remains to be disposed of, when breathing and metabolism are normal The kidney is able to do this by two mechanisms : (1) The formation and secretion of free hydrogen ions ; and (2) the formation and secretion of ammonia which combines with a hydrogen ion to form ammonium.

The amount of alkali that must be added to urine to return the *p*H to that of plasma is a measure of the nett quantity of free hydrogen ions which have been excreted in the urine and is known as the titratable acidity. The sum of the urinary titratable acidity and ammonium is a

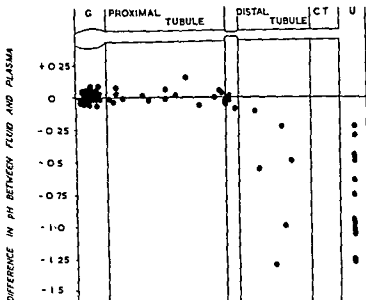


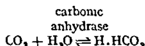
Fig 21 *p*H of the fluid obtained with micropipettes at different sites in the frog nephron compared to the *p*H in the plasma G = glomerulus, C T = collecting tubule, U = urine, (Montgomery and Pierce, 1937, *Amer J. Physiol*)

measure of the kidney's secretion of hydrogen ions, i e. its contribution towards preventing the internal environment from becoming acid

Free Hydrogen Ion Excretion and Bicarbonate Reabsorption

The secretion of hydrogen ions into the distal tubular fluid (Fig 21) not only permits the excretion of free hydrogen ions but it is also necessary for the reabsorption of sodium bicarbonate, and it is responsible for generating fresh bicarbonate (Fig. 22).

The hydrogen ion concentration of the distal tubule cell is increased by hydration of carbon dioxide, a reaction which is greatly accelerated by the high concentration of carbonic anhydrase these cells contain, i e



$$CO_2 + H_2O \underset{}{\overset{\text{carbonic anhydrase}}{\rightleftharpoons}} H.HCO_3$$

Some of the carbonic acid then dissociates into hydrogen and bicarbonate ions, and these additional hydrogen ions become available for secretion into the tubular fluid There they are exchanged for sodium

ions which enter the tubule cell. Some of the hydrogen ions in the tubular fluid are excreted in the urine in combination with a fixed acid, particularly phosphate. Others combine with the bicarbonate ions in the fluid to form carbonic acid but, owing to the presence of carbonic anhydrase in the tubular fluid, the $H.HCO_3$ is converted into H_2O and CO_2, and the CO_2 diffuses back into the tubule cell where it is either reutilised or passes into the blood. The sodium ions which have entered the cell combine with the intracellular bicarbonate ions and are reabsorbed into the blood as sodium bicarbonate (Fig. 22).

It is probable that the intracellular concentration of hydrogen ions

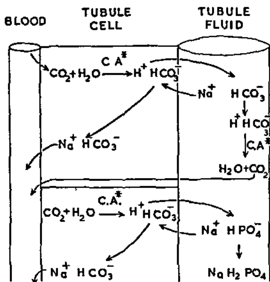


FIG 22 Secretion of hydrogen ions in the distal tubule and bicarbonate reabsorption and generation Note that the excretion of titratable acidity (free hydrogen ions) is chiefly in the form of acid phosphate, and that the formation of this salt is accompanied by the generation of fresh bicarbonate ions.

in the tubule cells determines the rate of hydrogen ion excretion and bicarbonate reabsorption ; and in turn it is likely that the intracellular concentration of hydrogen ions usually follows changes in the concentration of hydrogen ions in the extracellular fluid There is also some evidence that the production of hydrogen ions by the hydration of carbon dioxide is controlled by the carbon dioxide tension (Fig. 23). In addition there exists a reciprocal relationship between urinary hydrogen and potassium excretion. If for instance, the cellular production of hydrogen ions is inhibited by the administration of a carbonic anhydrase inhibitor such as acetazoleamide (Diamox), the excretion of potassium rises as the excretion of hydrogen ions falls.

Clinically the effects of these mechanisms can be observed in the varying forms of acidosis and alkalosis

Acidosis. In a respiratory acidosis (e.g. emphysema) there is a rise in the plasma concentration of hydrogen ions and carbon dioxide tension. Both factors tend to increase the concentration of hydrogen ions in the tubule cell, so that the excretion of hydrogen ions increases and there is a greater reabsorption of bicarbonate; the plasma will therefore tend to become less acid In an acute respiratory acidosis a simultaneous diminution in the excretion of sodium and potassium can also be demonstrated.

In a metabolic acidosis (e g. diabetic ketosis or ammonium chloride administration) there is also an increased concentration of hydrogen

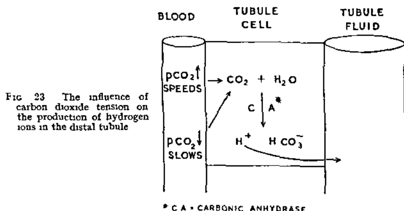


FIG 23 The influence of carbon dioxide tension on the production of hydrogen ions in the distal tubule

ions in the plasma, but because of the accompanying hyperventilation, the carbon dioxide tension is *reduced.* Nevertheless the tubules again increase the excretion of hydrogen ions and the reabsorption of bicarbonate. It appears therefore that in a metabolic acidosis the inhibitory effect of the reduced carbon dioxide tension on the intracellular production of hydrogen ions is swamped by the persistent rise in extracellular fluid hydrogen ion concentration. When the plasma bicarbonate concentration falls below 25 mEq /l the urinary excretion of bicarbonate bound to metallic cations ceases altogether (Fig 24) The maximum acidity which the tubule can sustain is approximately pH 4 6, which seriously limits the kidney's ability to excrete large quantities of free hydrogen ions, unless there are large volumes of urine, as in diabetic ketosis.

The kidney's capacity to deal with a metabolic acidosis is entirely

dependent on tubular function, i.e. the tubule's ability to excrete hydrogen ions and ammonia.

Alkalosis. When there is a respiratory alkalosis (e.g. voluntary hyperventilation, or excessive artificial ventilation in severe poliomyelitis) there is a fall both in the plasma hydrogen ion concentration and the carbon dioxide tension. Both these factors will decrease the availability of the hydrogen ions in the tubule cell so that less hydrogen ions are excreted and bicarbonate reabsorption is decreased; the plasma will therefore tend to become less alkaline. In an acute respiratory alkalosis a simultaneous increase in the excretion of sodium and potassium can also be demonstrated.

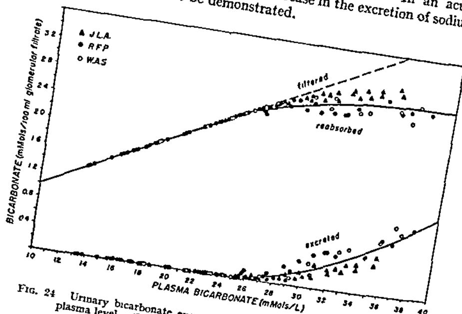


FIG. 24 Urinary bicarbonate excretion and reabsorption as a function of plasma level (Pitts, Ayer and Schiess, 1949, *J. clin. Invest.*)

In a metabolic alkalosis (e.g. sodium bicarbonate administration) there is also a fall in hydrogen ion concentration but, because of the accompanying hypoventilation, there is a *rise* in the carbon dioxide tension. The rise in carbon dioxide tension does cause a slight increase in bicarbonate reabsorption but, when the plasma bicarbonate concentration rises above 27 mEq/l., bicarbonate reabsorption cannot increase further and urinary excretion of bicarbonate bound to metallic cations then equals the increasing quantities which are filtered. In contrast to metabolic acidosis therefore, which is controlled by tubular mechanisms, the ability of the kidneys to control a metabolic alkalosis is directly related to the glomerular filtration rate. This is particularly

relevant when a patient suffering from mild renal failure is inadvertently given large amounts of sodium bicarbonate, e.g. for a gastric ulcer.

Ammonia Excretion

Ammonia is continually formed in the distal tubule cell (Fig. 25) from glutamine, a process which is accelerated by the high concentrations of intracellular glutaminase ; these cells also contain α amino

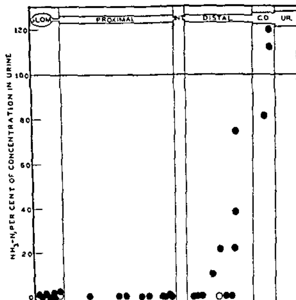


FIG [illegible]

oxidases which convert α amino acids into additional ammonia (Fig. 26). In the tubular lumen the ammonia is trapped by combination with hydrogen ion to form ammonium Urinary ammonium excretion is inversely related to the *p*H of the urine and ceases when the urine becomes alkaline. The increase in ammonium excretion which occurs as the urine *p*H falls is due in part to an increased diffusion of ammonia from the tubule cell into the tubular fluid But if the urine remains persistently acid the amount of ammonium excreted continues to rise

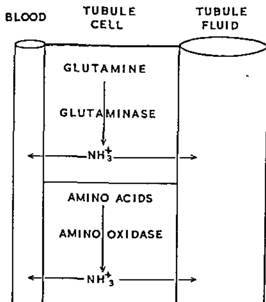


Fig 26 Ammonia production in the distal tubule, the diffusion of ammonia into the tubular fluid increases as this fluid becomes increasingly acid and thus the extent of ammonium excretion is related to the tubule's ability to secrete hydrogen ions

after the *p*H of the fluid has reached its minimum ; this is due to an increasing concentration of glutaminase in the tubule cells

In normal circumstances the daily excretion of ammonium and free hydrogen ions is approximately the same (i e. 20–30 mEq of each) When there is a need for an increased excretion of both (as in diabetic ketosis) the increase in ammonium greatly exceeds that of free hydrogen

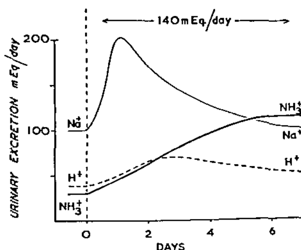


Fig. 27 The effect of 140 mEq/day of ammonium chloride by mouth on the urinary excretion of sodium, hydrogen and ammonium in a normal subject.

ions. Ammonium excretion may reach 400 mEq /day whereas the simultaneous excretion of free hydrogen ions will only be 70–100 mEq / day. These are very high excretion rates and are rarely seen except in prolonged diabetic ketosis. The response of a normal person to large quantities of ammonium chloride is illustrated in Fig. 27. It can be seen that after a delay of five days the ammonium excretion is about three times greater than that of free hydrogen ions.

Procedure Used to Estimate the Tubule's Ability to Excrete an Acid Urine and to Excrete Hydrogen Ions and Ammonia

The tubule's capacity to excrete hydrogen ions and ammonia is estimated by measuring its response to the oral administration of ammonium chloride The ammonium chloride molecule is metabolised to urea and HCl The addition of these hydrogen ions into the extracellular fluid tends to make it acidotic, and in order to compensate for this tendency the kidney excretes increasing quantities of hydrogen ions both as free hydrogen ions and as ammonium, and the urine becomes increasingly acid The maximum acidity is reached in three to four days after the beginning of ammonium chloride administration, while ammonium excretion takes four to five days to reach its peak. The chloride ions are also eliminated through the kidney , at first these are excreted with almost equal quantities of sodium, but very soon the initial increase in sodium excretion subsides as the chloride is increasingly " covered " by hydrogen and ammonium ions

Following two to three days' control observations, ammonium chloride is given by mouth in doses of 7 5 g (140 mEq) per day for five days (Fig. 27) This is given in divided doses throughout each day , most patients can manage this amount without trouble, but in some it causes gastritis with epigastric pain and nausea. To avoid this complication it is best to give the ammonium chloride as a solution, though it has a most unpleasant taste , capsules are unsuitable unless taken with large amounts of water for they are liable to dissolve on one spot of the gastric mucosa and cause pain ; enteric coated tablets often appear intact in the stools.

From the third to the fifth day, daily measurements of the following are made ·

1 24-hour urinary ammonium excretion
2 24-hour urinary hydrogen ion excretion (titratable acidity)
3 Urine *p*H.
4 Plasma bicarbonate and chloride.

At the end of four to five days the daily combined excretion of ammonium and hydrogen ions should rise above control values by

about 120 mEq., urine *p*H should fall below 5·0 (it is important that this estimation be done with a *p*H meter and not an indicator). If the renal response is normal, plasma bicarbonate and chloride concentrations rarely change and should not alter by more than 4 mEq./l.

There is another quicker method for testing these functions which is particularly useful as a screening test, or when it is considered inadvisable to give large amounts of ammonium chloride. A single dose of 7·0 g. of ammonium chloride (in capsules of 0·5 g.) is given over a 90 minute period in the early morning, together with a litre of water; the effects on the urine persist thereafter for about eight hours. During this time the urine *p*H should fall below 5·3, total acid excretion should rise above 15 μEq./min., and the ammonium excretion above 30 μEq./min.

If the patient has a spontaneous metabolic acidosis of more than seven days' duration his kidneys may be assumed to be responding to their maximal ability, and estimation of urine *p*H and hydrogen ion and ammonia excretion may be undertaken without ammonium chloride loading.

The ability to reduce the urine *p*H normally is impaired when there is a primary inborn tubular defect (Renal Acidosis) (p. 163), potassium deficiency (p. 150) and in certain cases of hypercalcuria (p. 155), while it remains normal in the chronic renal failure which accompanies loss of nephrons (p. 124). An impaired ability to excrete hydrogen ions at a normal rate occurs in renal acidosis, potassium deficiency, hypercalcuria and chronic renal failure. Finally, ammonia excretion is reduced in renal acidosis, in some cases of hypercalcuria and in chronic renal failure, whereas it is normal in potassium deficiency.

SODIUM EXCRETION

Sodium is the principal solid constituent of the extracellular fluid the volume and osmolarity of which are closely related to the amount of sodium it contains. In man, except for acute changes, there is overwhelming evidence that sodium excretion is unrelated to the rate of glomerular filtration, for patients with chronic renal failure keep in sodium equilibrium though they have extremely low glomerular filtration rates. Variations in sodium excretion are therefore related to changes in tubular reabsorption or secretion. It is generally considered that approximately 80 per cent. of the sodium that is filtered is reabsorbed together with chloride in the proximal tubule. Variations in sodium excretion are probably due to changes in the amount reabsorbed from the 20 per cent. that passes into the distal tubule where the reabsorptive mechanism is closely related to the tubular secretion of hydrogen ions and potassium. There is also some evidence from

animal experiments that at least a part of the sodium which appears in the urine may have been *secreted* by the tubules

Many physiological factors influence the urinary excretion of sodium, including blood volume, cardiac output, posture and emotion but the renal mechanisms concerned are obscure.

Aldosterone appears to be a specific agent for decreasing sodium excretion, and although cortisone and hydrocortisone frequently have a similar effect, these sometimes produce an *increased* excretion The presence of cortisone is necessary for the changes in sodium excretion which take place as a result of blood volume changes, but cortisone itself is not the substance which is directly responsible for the alterations in tubular function which occur. This phenomenon is sometimes called the "permissive" action of cortisone, it is not confined to tubular function.

An osmotic diuresis is always associated with an increase in salt excretion, a phenomenon which is occasionally of great clinical importance, e.g in diabetes. The changes in salt excretion produced by changes in blood volume and central nervous system disturbances are discussed in later sections ; it is possible that the tubules' handling of sodium ions may occasionally be directly affected by the renal nerves.

Procedure Used to Test the Tubule's Ability to Control Sodium Excretion

The efficiency of the tubules' ability to control sodium excretion can be tested either by increasing or decreasing the intake of sodium An excess of sodium, however, is rarely given, for an inability to excrete a sodium load is more frequently due to extrarenal influences stimulating the tubules to retain sodium (i e cardiac failure, liver failure, etc.) than to renal disease itself The dangers which follow an inability to excrete a sodium load may also be more sudden in onset, dangerous, and difficult to treat than those which may accompany sodium deficiency

Reducing the intake of sodium is a more specific test of intrinsic tubular abnormality. The patient is placed on a normal ward diet containing about 100 mEq of sodium per day, and the daily urinary sodium excretion is estimated for a control period during which it should (in the absence of diarrhœa or much sweating) be approximately 15 mEq /day less than the intake (to allow for loss in sweat and fæces) The dietary intake of salt is then reduced to about 20 mEq /day, which is the content of the average hospital "salt-free" diet Within three to four days urinary sodium excretion should also be down to 20 mEq. per day. As a rough indication the test can be performed by estimating urinary chloride concentrations using Fouchet's clinical side-room technique. On a low salt diet the concentration of chloride should not be more than 1 g /l. when S G is 1010 or greater.

Apart from Addison's disease and severe glycosuria, an inability to conserve sodium is seen occasionally in chronic renal failure, particularly with chronic pyelonephritis (p 224) ; it also occurs sometimes during the diuretic phase of acute renal failure, and very rarely as a result of a primary disturbance of tubular function (Renal Acidosis, p. 163).

POTASSIUM EXCRETION

Potassium is the principal intracellular cation. It should be remembered that in this respect the cells of the tubules are the same as other cells.

It has recently been shown both by direct tubular puncture and by indirect experiments, that the potassium that is filtered at the glomerulus is probably all reabsorbed in the proximal tubule, and that the amount which eventually appears in the urine is actively secreted by the distal tubule As with sodium, therefore, glomerular filtration rate is unrelated to potassium excretion ; a point of the greatest importance to patients suffering from most forms of chronic renal disease and in whom glomerular filtration rate is severely impaired

There is evidence that some of the mechanisms responsible for potassium secretion are also related to the distal tubular reabsorption of sodium and secretion of hydrogen ions (see above) When sodium is reabsorbed from the distal tubular lumen it is exchanged for hydrogen or potassium ions secreted from the tubule cell. The rates of secretion of these two ions are influenced by many factors and have an *inverse* relationship One of these factors is the relative concentration of each ion in the tubule cell, i e when the supply of intracellular hydrogen ions increases or the concentration of potassium ions diminishes, potassium secretion decreases

Many abnormal conditions are accompanied by a temporary increase in potassium excretion. Sometimes it occurs in relation to a rise in plasma potassium caused by a shift of potassium from the intracellular to the extracellular space.

Procedure Used to Test the Tubule's Ability to Control Potassium Excretion

Unlike sodium, where the serum concentration tends to remain unchanged or *fall* with sodium retention, serum potassium *rises* with potassium retention This makes the testing of the kidney's ability to deal with an increased potassium load a potentially dangerous procedure, and it is therefore never attempted. Urinary excretion is the main route of potassium elimination, and if the serum potassium is found to be persistently raised it is clear that there is a tubular defect of potassium excretion

To show that there is a potassium deficit and that it is due to exc urinary loss is more difficult. Except when *serum potassium is* bel 3 mEq./l. a low concentration is uncertain evidence of potassi deficiency; though it is more likely if there is a concomitant rise serum bicarbonate (p. 167) If potassium depletion is suspect evident, and there is no obvious diminished intake, or leak from *intestinal tract, it is almost certain that it is due to abnormal loss in* urine This is confirmed by measuring the oral intake of potassi and its output in the urine.

The patient is placed on a normal diet containing 80–100 mEq potassium per day and the daily urinary potassium excretion measured for a control period, during which it should be 10–20 ml less than the intake (this small amount is eliminated in the fæces) the urinary excretion is greater than the intake, particularly when plasma potassium concentration is low, there is unequivocal evide of a urinary leak of potassium. The following relationship betw the lower concentrations of plasma potassium and the urinary excret of potassium, when the patient is eating a normal ward diet, is a relia substitute for a balance study. If there is a renal leak of potassi and the plasma concentration of potassium has fallen to 3 mEq /l. lower the urinary excretion of potassium will be greater than 20 mE 24 hours; whereas if the potassium deficiency is due to some ot cause (such as diarrhœa) the urinary excretion of potassium at th low plasma potassium concentrations will be less than 20 mEq./24 hou This distinction persists even when potassium deficiency has caus severe renal functional impairment (p. 150).

If the findings on a normal diet are within normal limits and ye urinary leak of potassium *seems very likely, the patient is placed o* low potassium diet, since in some instances the tubular abnormality m only become apparent when the potassium intake is reduced. Or diet low in potassium the urinary excretion of potassium should fall 20 mEq /day within three to four days It is difficult to obtain low values, even in normal subjects, on an experimental diet free potassium except after an inconveniently long period of deprivatio

A finding of excessive urinary loss of potassium is an indication renal disease, either congenital (Renal Acidosis, p 163) or acquir *except for those rare occasions when it is due to Aldosteronism (p. 27* Cushing's disease (p. 271), or the prolonged administration of stero

CALCIUM EXCRETION

Calcium reabsorption from the glomerular filtrate mainly occurs the proximal tubule, though the initial functional disturbance associat

with hypercalcuria is an impairment in the ability to concentrate, which is a collecting, and possibly distal, tubular function.

A high urinary excretion of calcium may occasionally be due to a primary disturbance of tubular function, but more often an increased urinary loss of calcium (stimulated by some extrarenal mechanism) is itself the cause of severe structural and functional disturbance (p. 154) Hypercalcuria always occurs if the concentration of plasma calcium is raised, but it may also be present when the plasma calcium is normal; with a primary tubular defect the plasma calcium is always either normal or low.

Procedure Used to Determine the Presence of Hypercalcuria

Hypercalcuria can be defined as the daily urinary excretion of more than 200 mg. of calcium when the diet contains less than 150 mg. When hypercalcuria is very great it is easily recognised, for upon adding Sulkowitch's* reagent to the urine a thick white precipitate will rapidly appear If this test is equivocal or negative it is necessary to do a balance study, and a simple way to do this is to place the patient on a rice diet. The rice is cooked in distilled water,† but salt can be added in normal amounts, and jams, sugar and fruit are allowed, drinking water must also be distilled. Such a diet contains about 90–130 mg. of calcium/day. The urine calcium excretion is estimated on the fourth day.

* *Sulkowitch's reagent*

Oxalic acid	2·5 g
Ammonium oxalate . . .	2·5 g.
Glacial acetic acid	5 ml.
Water to	150 ml

Add 2 ml of reagent to 5 ml. of urine.

† London tap water contains 5 mg /100 ml of calcium

PHOSPHATE EXCRETION

The most important feature of phosphate excretion is that it is directly related to the glomerular filtration rate. Tubular reabsorption of phosphate may rise or fall, depending particularly on the concentration of circulating parathormone, but it is never able to fall sufficiently to compensate for a gross reduction in glomerular filtration rate. Advanced renal failure therefore is associated with a rise in plasma phosphate.

Very occasionally an intrinsic tubular defect of phosphate reabsorption may cause a urinary phosphate leak with a lowered plasma phosphate concentration (and a normal serum calcium). In such cases the difficulty is to decide whether the altered plasma phosphate is due to a primary disturbance of the tubules or to hyperparathyroidism

(p 157) The distinction is usually made on the fact that a primary tubular defect of phosphate absorption is frequently associated with other evidence of abnormalities of tubular function such as glycosuria and amino aciduria

AMINO ACID EXCRETION

With the usual paper chromotographic technique, three groups of amino acids are seen in the urine

1. Glycine and taurine.
2. Alanine.
3. A group which includes valine, β amino-iso-butyric acid, histidine and methylhistidine. These can be separated by more elaborate chromotography Many other amino acids are present in normal urine but they are in insufficient concentrations to be detected by routine methods

When there are abnormalities of amino-acid excretion they are usually divisible into two categories·

(a) Excess excretion of cystine, lysine and arginine, i e cystinosis where these are the only tubular abnormalities.

(b) Excess excretion of all amino acids as in the Fanconi syndrome when there are also many other tubular abnormalities

MAXIMAL CAPACITY OF THE TUBULES TO TRANSPORT GLUCOSE AND PARA-AMINO HIPPURIC ACID

The capacity of the tubules to reabsorb or secrete certain substances is limited, and a measure of this is obtained by estimating the maximal amount that the tubules can either secrete or reabsorb in one minute This amount is referred to as the Tm of that substance (derived from the words " tubule " and " maximal ") , it has a certain value in giving quantitative expression to the total mass of functioning tubular cells, but it is scarcely ever measured in clinical work, for the precision which it contributes is rarely needed It is discussed here mainly because an understanding of Tm is a help in the study of renal function

Reabsorption Tm

The Tm of glucose (Tm_g) is a good example of a reabsorptive Tm When blood glucose is within normal limits it is unusual for there to be glucose in the urine, since all the filtered glucose has been reabsorbed To determine Tm_g an intravenous infusion of glucose is given at a rate

sufficient to raise the blood glucose substantially. Glycosuria occurs and the amount of glucose reabsorbed is calculated as follows :

glucose filtered — glucose excreted = glucose reabsorbed

or

$$GFR \times P_g - U_g \times V = T_g,$$

where GFR is glomerular filtration rate per minute, P_g is plasma glucose concentration, U_g the urine glucose concentration, V the rate of urine flow, and T_g the rate of glucose reabsorbed as mg. per minute The rate of glucose administration continues to be increased in a stepwise manner and the measurements are repeated ; blood glucose and glycosuria increase steadily, but there comes a point beyond which the quantity of glucose reabsorbed remains constant ; this is the Tm_g, and in normal man is 323 $\pm$ 64 mg /min.

The plasma glucose concentration at which glucose first appears in the urine is sometimes referred to as the renal threshold for glucose. *This level is roughly correlated with Tm_g but is a less constant value, for it is influenced by alterations in glomerular filtration rate.* At the renal threshold for glucose the quantity of glucose being presented to the tubules by the glomerular filtrate is only just sufficient to exceed the tubule's ability to reabsorb all the glucose passing through ; if plasma glucose remains unchanged but there is a fall in filtration rate, no glucose will appear in the urine and the renal threshold will have altered. But when estimating Tm_g the blood glucose concentration is raised to such high values that, so long as a nephron has some filtration, the amount of glucose being presented to the tubules for reabsorption is far in excess of its maximum reabsorbing capacity ; in this way alterations in glomerular filtration rate cannot influence the amount reabsorbed.

Secretion Tm

In this context a substance is considered to be secreted by the tubules only if the amount excreted in the urine is greater than that which has been filtered. This is, of course, a convenient but grossly arbitrary definition, for some substances which are actively secreted by the tubules (e.g potassium) have a total urinary excretion which is usually less than that which has been filtered (p. 54) To measure the true amount secreted, therefore, it would be necessary to know the amount which has been reabsorbed, and in ordinary circumstances this is not possible.

Those substances which have the greatest rate of tubular secretion according to the definition given above are those which are not normally present in body fluids, and include diodone, phenol red, penicillin and

INTERPRETATION OF THE RESULTS OF THE TWO MOST WIDELY USED TESTS OF RENAL FUNCTION, i e, GLOMERULAR FILTRATION RATE AND THE ABILITY TO CONCENTRATE

The information derived from these two tests alone allows a certain measure of subdivision of renal disorders

Glomerular Function (Filtration rate)	*Tubular Function (Ability to concentrate)*	*Interpretation*	*Renal Disorder*
Decreased	Decreased	Number of functioning nephrons diminished	Chronic glomerular nephritis, polycystic kidneys, etc, etc
		or	
		Both glomerular and tubular function impaired, number of functioning nephrons variable	1 Severe urinary obstruction 2 Severe renal ischæmia, e g acute renal failure from loss of blood 3 Severe electrolyte abnormality, e g potassium deficiency and hypercalcæmia 4 Renal poisons, e g acute renal failure from the ingestion of mercury
Normal or slightly decreased	Decreased	Tubular function definitely impaired, glomerular function normal or impaired to a much smaller extent than tubular function	1 Urinary tract obstruction, either recent, moderate or unilateral 2 Chronic pyelonephritis in its early stages 3 Moderate electrolyte abnormality, e g potassium deficiency and hypercalcæmia 4 Inborn functional defect of renal tubules, e g Fanconi's syndrome 5 Compulsive polydipsia
Decreased	Normal	Glomerular function impaired, tubular function normal	1 Moderate acute renal ischæmia, e g hæmorrhage insufficient to cause acute renal failure 2 Acute nephritis

6

DIURNAL RHYTHM

THE urinary excretion of water and most electrolytes is normally greater during the day than at night, a fortunate phenomenon which ensures that the night's repose shall be undisturbed. This pattern is not only due to the fact that fluid and food are taken during the day ; it will persist even if identical quantities of food and water are ingested at regular intervals throughout the 24 hours. As the evening approaches and during the night, the excretion of sodium, potassium, bicarbonate and chloride ions gradually diminishes, while the pH of the urine falls, and its concentration rises ; the process is reversed in the morning (Fig 28).

The mechanism responsible for this rhythm is unknown ; it has been shown that there is a small nocturnal fall in glomerular filtration rate, but this cannot explain all the changes that occur ; for instance, the excretion of phosphate *increases* at night and diminishes during the day It is possible that the changes in water excretion, and particularly *the changes in urine concentration, follow a diurnal alteration in* antidiuretic hormone excretion There is no doubt that an antidiuretic mechanism is present, for at night a large drink of water only produces a small increase in urine flow The changes in electrolyte excretion are preceded, by a few hours, by similar fluctuations in steroid excretion It is probable that this is only coincidental, for it fails to explain why *the changes in sodium and potassium excretion should be parallel ;* it has also been reported that under certain conditions the excretion of steroid will rise gradually throughout the day and night, and yet the diurnal rhythm of electrolyte and water excretion continues uninterruptedly.

A normal diurnal rhythm persists during undernutrition, water deprivation, salt deprivation, the sustained action of pitressin and a temporary disturbance of sleep rhythm For instance, a person going from east to west on a ship across the Atlantic will show a peak of electrolyte excretion one hour (ship time) earlier each day. But the clock " gains " an hour each day so that in fact the diurnal rhythm changed in relation to European time. Reversal or abolition

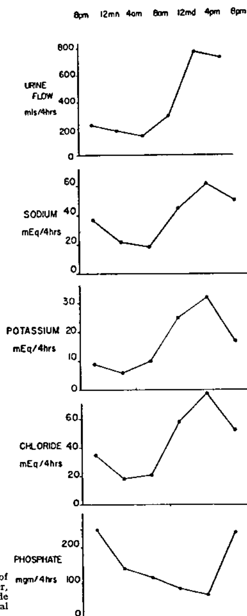


FIG 28 Diurnal rhythm of urinary excretion of water, sodium, potassium, chloride and phosphate in a normal subject

syndrome and malnutrition. In these conditions the volume of
passed at night may be equal to or exceed the daytime total (Fig
It may also be reversed in chronic renal failure, Addison's disease
following a head injury. In a normal person the diurnal rhythm
be abolished and occasionally reversed by the administratio
cortisone.

A knowledge of a patient's pattern of electrolyte and
excretion may sometimes be of help in treatment. An oedem
person with a reversed rhythm, for instance, may only have a di
following the administration of a mercurial, if it is given in the eve

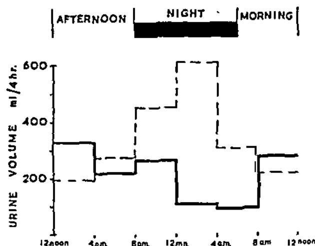


FIG 29 Pathological reversal of the diurnal rhythm of urinary excretion of water (- - - -) compared with the normal rhythm (——)

rather than in the morning. Or, if water and electrolytes are b
given intravenously to a patient about whom there is some fear
he may become overloaded, it is best to start the infusion at a
when there is a spontaneous increase in electrolyte and water excre

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7

RENAL FUNCTION IN RELATION TO AGE

Renal Function in the Fœtus

For obvious reasons there is not a great deal known about fœtal renal function The outstanding fact is that fœtal urine is hypotonic to its own plasma This suggests that the development of that part of the nephron that is concerned with diluting the isotonic tubular filtrate (p. 34) is developed before the collecting tubule is able to respond to antidiuretic hormone.

Renal Function in Infancy

It is evident that the infant's kidney is perfectly satisfactory for normal purposes. When called upon to deal with an emergency however, it is less adaptable than that of an adult, e.g when there is an acute loss of salt and water

Glomerular filtration rate, calculated on a surface area basis, is proportionately less than in an adult and yet the concentration of urea in the blood is lower. This is due to the relatively larger quantities of nitrogen that are being retained at this time of life, and in normal circumstances the low glomerular filtration rate is perfectly adequate to dispose of the small amount of waste products of protein catabolism The hazards of this situation are evident when the child becomes ill and ceases to store nitrogen A sharp increase in protein catabolism is then liable to produce a rapid rise in blood urea and, if protein administration is continued in an attempt to "feed him up," the blood urea may rise rapidly though there has been no alteration in the glomerular filtration rate.

Tubular control of sodium and water excretion shows little elasticity. An inadequate fluid intake or an attack of diarrhœa may lead to severe dehydration and yet the urine flow remains almost unchanged, owing to the tubule's poor response to antidiuretic hormone. Alternatively an excessive administration of fluid may cause over-hydration, for the elimination of a water load is slow.

The tubule has little control over sodium excretion. During a negative balance of sodium, as in diarrhœa, substantial urinary excretion of sodium continues ; and if excess sodium is given intra-

venously the rise in excretion is slow and inadequate so that oedema develops.

The other tubular functions which have been found to be relatively less efficient than in an adult are the ability to excrete a highly acid urine, ammonia production, and secretion Tm (p. 58)

Renal function becomes comparable to that of an adult between the sixth and twenty-fourth month.

Renal Function During Senescence

After the age of 30 there is a gradual reduction in renal functional capacity. The functions which have been studied include glomerular filtration, renal blood flow and secretion Tm, urea clearance, and the ability to concentrate

that every function is involved. It is certainly very noticeable that elderly patients are not able to concentrate their urine to the same extent as adolescents.

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8

THE RENAL CIRCULATION

At rest about one-fifth of the cardiac output flows through the kidney, the normal renal blood flow being approximately 1,100 ml /min It is a greater irrigation per unit weight of tissue than any other organ. The reason for this is not understood for, though a substantial and sustained reduction in renal blood flow is always associated with some fall in glomerular filtration rate, renal function in all other measurable respects may remain perfectly normal. In the following discussion it is to be remembered that changes in renal blood flow are generally accompanied by similar changes in the glomerular filtration rate, though frequently the degree of change may be different.

SOME FACTORS WHICH CAUSE A REDUCTION IN RENAL BLOOD FLOW

The normal renal blood flow is very great, consequently if a change does occur, the flow is nearly always reduced The upright posture, undernutrition, exercise, pain, heat, adrenaline and advancing years are some of the physiological factors associated with such a reduction. The pathological causes are discussed below.

Circulatory Insufficiency

Clinically the most frequent cause of a fall in renal blood flow is circulatory insufficiency Contraction of the blood volume and cardiac failure both cause renal vasoconstruction and a fall in renal blood flow, whether or not there is a concomitant decrease in blood pressure

Contraction of the blood volume may be secondary to traumatic, surgical or spontaneous bleeding, acute hæmolysis, severe diarrhœa and vomiting, burns, or negative protein balance. Sudden changes in blood volume produce the most marked changes in the renal circulation, but there is a delay between the time of the hæmorrhage and the onset of renal vasoconstriction A hæmorrhage which is severe enough to induce peripheral vasoconstriction, with pallor and coldness of the hands, feet and face, may not cause a fall in renal blood flow within the next one to two hours. If, however, the blood volume remains reduced for four to seven hours there is severe renal vasoconstriction, which

may be sufficient to cause necrosis of the renal cortex. The cause of this vasoconstriction is humoral (at least 17 renal vasoconstrictors have been identified following hæmorrhage), and this may be the reason why the constriction takes a few hours to become maximal Therapeutically the delay is sometimes an advantage, for early transfusion may prevent the onset of severe renal ischæmia, but conversely once ischæmia has developed, transfusion is only associated with a slow recovery; the ischæmia continuing for several hours though the blood volume is normal

Cardiac failure induces renal vasoconstriction both when the cardiac output is low (when the fall in renal blood flow is proportionately greater than the fall in cardiac output) and when the output is high, as in cor pulmonale and thyrotoxicosis In the latter the cardiac output may be doubled and yet the renal blood flow may fall to 20 per cent. of its normal value The cause of this vasoconstriction is uncertain, but the inability of a high spinal anæsthetic to alter the renal blood flow in established cardiac failure suggests that it may be humoral This is supported by the finding that some increase in renal blood flow occurs following the administration of the adrenaline antagonist Dibenamine Large increases in renal venous pressure have been found to produce transient reductions in renal blood flow But this is not the cause of the fall in renal blood flow in cardiac failure, for the renal venous pressures usually encountered are not in this high range, and in chronic heart failure the venous pressure and renal blood flow may vary independently

A teleological explanation for the renal vasoconstriction which occurs with circulatory distress is that it maintains the arterial pressure and switches the available cardiac output to organs which are less able than the kidney to function with a reduced blood flow.

Acute Uterine Catastrophies

There is a close association between the incidence of abortion accidental hæmorrhage, and eclampsia on the one hand and severe renal ischæmia on the other Abortion is the most frequent cause of acute renal failure.

In many of these conditions hæmorrhage must be partly responsible for the renal ischæmia, but it is probable that occasionally other mechanisms are also involved It has been demonstrated in experimental animals that an acute rise in intra-uterine pressure causes a marked fall in renal blood flow, if such a mechanism is present in man it may be an important contributory factor in the causation of renal ischæmia in some of the conditions mentioned above (e g concealed accidental hæmorrhage)

Electrolyte and Endocrine Abnormalities

Most forms of electrolyte abnormalities cause a reduction in renal blood flow With simple water depletion, or with combined salt and water depletion, this reduction is caused by the contraction of the blood volume. But with water intoxication due to salt loss, or excess water intake the mechanism is obscure. Potassium deficiency and hypercalcæmia also cause a fall in renal blood flow. Initially these circulatory changes are quickly and completely reversible ; if, however, they are prolonged and are associated with the development of structural changes, recovery will be incomplete.

The renal blood flow is also reduced in hyper- and hypo-adrenalism, hypopituitarism and myxoedema.

Circulating Vasoconstrictors other than those Produced by the Endocrine Glands

Free circulating hæmoglobin is the most important of these substances It may cause intense renal ischæmia particularly in incompatible blood transfusions and blackwater fever (pp 283–4)

Exogenous substances which reduce the renal blood flow include a variety of cytotoxic poisons such as carbon tetrachloride, corrosive sublimate (mercuric chloride), propylene glycol, etc. Frequently tubular necrosis follows, both from direct action of the poison on the cells and from intense renal ischæmia (p 106)

Some infections such as Weil's disease and scrub typhus are also associated with severe reductions in renal blood flow.

Disorders of the Renal Vasculature

Atheroma of the large intrarenal arteries may occasionally lead to wedge-shaped loss of renal parenchyma and a substantial fall in renal blood flow , while hypertension (particularly the malignant form), polyarteritis nodosa, eclampsia, diabetes and amyloidosis frequently produce such obliterative changes in the arterioles and glomerular capillaries that severe fatal renal ischæmia may result. Changes in the renal vessels in diffuse lupus erythematosus and scleroderma may also lead to renal failure The acute glomerular capillaritis of acute nephritis does not usually affect the renal blood flow, but there are occasional instances of severe renal ischæmia.

Gradual Destruction of the Renal Parenchyma as a Cause of a Decrease in Renal Blood Flow

Loss of nephrons is at first compensated for by an increased flow of blood through the remaining nephrons, e.g. the changes which occur following unilateral nephrectomy. Eventually, however, with further

loss of nephrons the renal blood flow inevitably diminishes Among the conditions which have not yet been considered and which produce a gradual destruction of the renal parenchyma there are: chronic glomerular nephritis, pyelonephritis, polycystic disease, congenital tubular disorders, renal tuberculosis and urinary tract obstruction

SOME FACTORS WHICH CAUSE RENAL HYPERÆMIA

These include cold, large protein intake, hyperpyrexia, sudden increase in blood volume, emotion, aminophylline derivatives, methedrine, magnesium sulphate, polycythæmia and pregnancy In general such increases in renal blood flow are of no clinical importance, though occasionally aminophylline is used to raise the renal blood flow and glomerular filtration rate when trying to obtain an adequate diuresis with parenteral mercurial preparations (p 312)

ADJUSTMENT OF THE RENAL CIRCULATION TO CHANGES IN HÆMATOCRIT

In the normal kidney the fall in hæmatocrit which occurs in anæmia is associated with a substantial decrease in renal blood flow, a small reduction in plasma flow and an almost unchanged glomerular filtration rate, when the hæmatocrit falls below approximately 20, however, the onset of cardiac failure causes the renal ischæmia to become much more pronounced and there is a marked reduction in plasma flow *and* glomerular filtration (Fig 30)

Conversely the rise in hæmatocrit which occurs in polycythæmia is associated with a substantial *increase* in renal blood flow, but again there is only a small reduction in plasma flow and an almost unchanged [illegible] to be sharply depressed

These changes suggest that the kidney is mainly concerned with the maintenance of a constant renal plasma flow and glomerular filtration, and not with the total renal blood flow The mechanisms responsible for these adjustments are not known, but they appear to be local in origin and unrelated to changes in cardiac output, clinically the important point is that such adjustments may take some days to complete.

In diseased kidneys these adjustments take place more slowly or not at all The result is that a perfectly justifiable transfusion for anæmia in chronic renal failure may be followed by a rapid deterioration in renal function. The explanation is as follows It has been

pointed out earlier that a reduction in glomerular filtration rate to 50 per cent of normal produces little absolute change in the blood concentrations of waste products, but with further reductions in filtration rate these concentrations rise steeply. If, therefore, owing to renal parenchymal destruction the glomerular filtration rate is low, it is clear that a *further small decrease in filtration will produce a large increase in blood concentrations of waste products*. Such a decrease in filtration may follow the rise in hæmatocrit which accompanies a

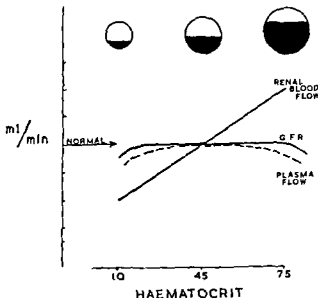


FIG 30 Schema of the changes in renal blood flow, plasma flow and glomerular filtration rate which occur in the normal kidney in response to changes in hæmatocrit The three circles illustrate what is presumably taking place in the renal vessels, i e the renal plasma flow remains constant because the diameter of the renal vessels varies directly with the changing fraction of red cells

transfusion ; it is due to the failure of the renal vessels to dilate sufficiently quickly to accommodate the rising fraction of red cells ; the renal plasma flow and filtration rate are automatically reduced and the patient may die of acute anuria. For the chronic anæmia of renal failure, therefore, transfusions should be given in small amounts at intervals of three to four days ; it is best to give packed red cells in order to minimise the risk of causing heart failure which is the other hazard of transfusing patients with renal failure. An estimate of glomerular function should be obtained between each transfusion.

ADJUSTMENT OF THE RENAL CIRCULATION TO CHANGES IN ARTERIAL PRESSURE

The rate of blood flow is related to the arterial pressure and the resistance of the vessels, i.e. $F = \frac{P}{R}$ where F = blood flow, P = arterial pressure and R = vascular resistance. Alterations in resistance are produced almost entirely by changes in the calibre of the vessels, i.e. by vasoconstriction and vasodilatation. Such changes usually occur as part of a general alteration in total peripheral resistance, e.g. hypertension and hæmorrhage are both associated with an increase in total peripheral resistance and, in each, renal vasoconstriction contributes to the increase. Occasionally, however, changes in renal resistance may occur which do not stem from some central demand for circulatory adjustment. For instance there are the changes in renal vascular resistance which accompany changes in hæmatocrit (see above), and the following changes which accompany alterations in arterial pressure.

It is well established that the kidney has an independent mechanism which alters the calibre of the renal vessels in response to changes in arterial pressure. This relationship between the rate of renal blood flow and the arterial pressure is most easily demonstrated in the isolated perfused dog's kidney, and is illustrated in Fig. 31. It can be seen that over a pressure range of about 0 to 90 mm Hg the blood flow rises with the pressure; from 90 to 200 mm Hg the flow remains relatively unaltered; and after 200 mmHg the flow rises once again. The exact mechanism responsible for these changes is obscure; it is not due to changes in the intrarenal pressure, and it appears to be an active process, for it is abolished by cyanide. It is probable that the alterations in vascular lumen occur on the afferent side of the glomerulus, for the glomerular filtration rate parallels the changes in the renal blood flow. This constancy of the renal blood flow is known as renal circulatory autoregulation.

Indirect evidence for the presence of a similar stabilising mechanism in the renal vasculature of man has been obtained on several occasions, though the exact range over which it occurs is not known. It must almost certainly be over a lower range than in the dog, for the mean blood pressure of dogs is higher than that of man. There is some evidence that renal circulatory autoregulation in man is present down to a mean arterial pressure of about 60 mm Hg. Such observations are difficult to obtain, for in most circumstances changes in arterial pressure produce a central demand for compensatory alterations in the peripheral resistance which have priority over purely local circulatory

reflexes ; the latter are best observed following small changes in arterial pressure produced by changes in cardiac output.

Teleologically this intrinsic pressure-flow relationship is difficult to understand. One suggestion is that it protects the glomerular filtration rate from the normal fluctuations in pressure, so that the tubules are presented with a continuous steady quantity of materials. As many of the factors which influence tubular function are slow to change the extent of their activity, a stability of this nature may be of value.

Clinically there are two aspects of this local pressure-flow relation-

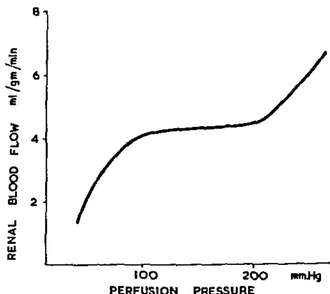


FIG 31 Renal circulatory autoregulation The relationship between the perfusion pressure (i e renal artery pressure) and the renal blood flow in a dog's kidney, showing the relative constancy of the blood flow when the perfusion pressure is between 100 and 200 mm Hg

ship which are of interest The first is purely speculative ; does this mechanism, which responds to a rise in arterial pressure by vasoconstriction, ever become so disordered in disease that excessive vasoconstriction occurs at normal blood pressures ? The other is more practical and is related to the treatment of hypertensive patients with hypotensive drugs. When renal function is substantially normal the renal blood flow and glomerular filtration rate remain unchanged as the blood pressure falls. But if there is evidence of renal damage (reduced glomerular filtration, etc) before the administration of the hypotensive agent the normal pressure-flow relationship may either

fail, or only become manifest after a long interval. In these circumstances glomerular filtration rate will fall, the blood urea rise steeply, and the patient may die of acute upon chronic renal failure It is always wise therefore to induce a fall in blood pressure gradually in such patients, and to repeat estimations of glomerular function at frequent intervals

SHUNTS

It has been claimed that in some circumstances, the cortex may become ischæmic because the blood which should have travelled to the cortex is shunted through the medulla This conclusion was first reached from observations made on experimental animals subjected to the following stimuli prolonged application of tourniquets to the hind limbs, bleeding, stimulation of the sciatic nerves and the administration of certain substances such as adrenaline, in large quantities During and immediately after stimulation the renal circulation was studied by means of angiographs, injections of methylene blue, and histological sections These techniques give an indication of the *distribution* of blood within the kidney at any one time, but are not measures of the *rate* of blood flow in any one place It was found that the stimuli were associated with the following change in the distribution of blood , the cortex contained less and the medulla more, that is, the cortex on section was pale and the medulla was dark Mainly from

There is much evidence however, that this assumption was unwarranted. It has been pointed out that to demonstrate that ischæmia is due to the opening of a shunt it is necessary to show that the decrease in flow in the ischæmic area is of the same order as the increase in flow in the shunt, i e if a large diversion of the normal cortical blood flow takes place it should be possible to demonstrate cortical ischæmia without significant reduction in renal blood flow But when renal blood flow is measured, the cortex becomes pale and the medulla dark only when the total renal blood flow is greatly reduced It is clear therefore, that the ischæmic pallor of the cortex cannot be due only to an increase in medullary flow, whether or not a small increase does occur. That such an increase is unlikely has been demonstrated with temperature measuring needles simultaneously recording from medulla and cortex ; for when the total renal blood flow is markedly reduced by nor-adrenaline, adrenaline and stimulation of the renal nerves the changes in temperature which take place (and which presumably reflect changes in blood flow) are the same in the two sites.

It has even been suggested that when there is pallor of the cortex and congestion of the medulla it is probable that there is no blood flowing through the medulla, for it has been found that indian ink injected intravenously may sometimes fail to appear in the medulla.

The importance of the observations which led to the renal shunt hypothesis is that they showed that in certain circumstances the cortex of the kidney has a disconcerting tendency to shut off its blood supply almost completely.

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9

THE KIDNEY AND HYPERTENSION

THERE are four important points to note when considering the relationship between the kidney and hypertension .

(1) Renal mechanisms concerned with hypertension have mainly been studied in animals.
(2) Renal disease in man is very frequently associated with hypertension
(3) Hypertension in man often causes renal disturbances.
(4) There is as yet, no evidence that essential hypertension in man is due to renal dysfunction.

EXPERIMENTAL HYPERTENSION IN ANIMALS

Renal Hypertension

It has been firmly established in experimental animals that partial occlusion of the renal artery is followed by hypertension In some animals both renal arteries must be occluded whereas in the rat it is sufficient to occlude only one renal artery (Fig 32) Hypertension does not appear to be due to renal ischæmia, for it can be induced by an occlusion which does not interfere with renal blood flow. An unchanged renal blood flow despite partial occlusion of the renal artery, may at first seem paradoxical, but it is probably maintained by renal circulatory autoregulation, the phenomenon discussed in the previous section (p 73). There is also evidence that hypertension will follow a partial occlusion of the renal artery even if the occlusion is adjusted so that the mean renal arterial pressure distal to the point of occlusion remains unchanged. It is concluded therefore that the hypertension which follows partial renal artery occlusion is due to the decrease in pulse pressure There is also some clinical support for this conclusion (see below)

The next steps in the initiation of hypertension following renal artery occlusion are more obscure. It has been demonstrated that soon after renal artery occlusion a substance produced by the kidney (renin) is released into the general circulation which reacts with a plasma globulin (plasma hypertensinogen) to form a vasoconstrictor (hypertensin) There is no doubt that this mechanism can cause transient

hypertension, but it is now accepted that the *maintained* hypertension of renal artery occlusion is unlikely to be due to an increase in circulating hypertensin, for after a few weeks there is no evidence of an overactive renin mechanism. It is probable therefore that other mechanisms are responsible for the persistent rise in blood pressure. Some authorities have claimed that one of these mechanisms is an adaptation of the circulatory baroreceptors to the higher levels of arterial pressure. There are, however, two other renal manipulations which cause a rise in blood pressure. One is known as *vicious circle*

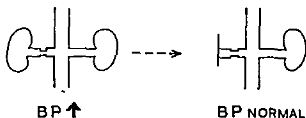


Fig 32. Renal hypertension.

renal hypertension, and the other as *renoprival hypertension* (to distinguish them from the hypertension which follows renal artery occlusion, i.e. *renal hypertension*). It is possible that the mechanisms which cause the blood pressure to rise in these manœuvres may also be concerned in maintaining the rise in blood pressure which follows renal artery occlusion.

Vicious Circle Renal Hypertension

This form of hypertension is intimately connected with renal hypertension and occurs in the following circumstances. If renal hypertension is induced in the rat by occluding only one renal artery, the subsequent removal of the occlusion, or of the " occluded " kidney, may or may not be followed by a return of the blood pressure to normal. The deciding factor is the extent of hypertensive vascular damage present in the untouched kidney (Fig. 33). Once again the mechanism responsible for the persistent hypertension is unknown. As it is related to the degree of vascular damage it has been suggested that perhaps the mechanism is the same as in renal hypertension ; the occlusion being produced by hypertensive vascular changes throughout the periphery of the renal arterial bed. If such a self-perpetuating hypertensive mechanism occurs in man it is clearly of the utmost therapeutic importance.

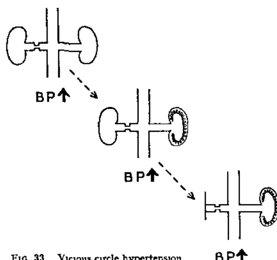
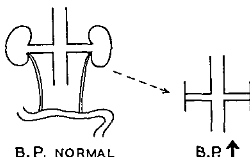


Fig 33 Vicious circle hypertension

Renoprival Hypertension

As the name implies, this form of hypertension follows bilateral nephrectomy. It cannot therefore be due to any pressor substance elaborated by the kidney. The alternatives are that it is due either to an extra-renal pressor substance which is usually disposed of by the intact kidney, or to the absence of a vasodilator normally produced by

Fig 34 Renoprival hypertension



the kidney. The former is the more likely and, as hypertension does not follow ureteric implantation into the bowel (Fig 34), or into the inferior vena cava, it seems that the kidney disposes of the extra-renal vasoconstrictor by destroying or neutralising it rather than by excreting it in the urine

The main speculation about renoprival hypertension is whether the mechanism of its production is the same as that responsible for renal and vicious circle hypertension, i e. can certain stimuli such as diminished pulse pressure inhibit the kidney's ability to control this extrarenal pressor system?

Experimental Hypertension and Adrenal Function

All three forms of experimental hypertension are greatly influenced by variations in adrenal function, or salt and water administration; for instance, adrenalectomy will prevent or abolish the hypertension. As hypo-adrenalism is known to cause hypotension this is not particularly surprising. It has been suggested that at all times the kidneys and adrenals combine in regulating the blood pressure, but there is at present insufficient evidence.

Possible Correlation Between Experimental and Clinical Findings

Statistically it is evident that in man renal disease is associated with hypertension, it is not unreasonable therefore, to suspect that some, if not all, the renal mechanisms which have been shown to produce hypertension in animals may eventually be proved to have their clinical counterpart. Some parallels can already be drawn.

ALTERATIONS IN PULSE PRESSURE

Following hæmorrhage, or acute reductions of the extracellular volume by vomiting and diarrhœa, the pulse pressure diminishes whether or not there is a fall in mean arterial pressure; in these circumstances there is evidence that the renin mechanism is stimulated and that the maintenance of the blood pressure is in part controlled by an increased quantity of circulating hypertensin.

A reduced pulse pressure to the renal arterial tree also occurs in coarctation of the aorta. In this condition, though there is no evidence that the renin mechanism is hyperactive or that the rate of renal blood flow is abnormal, it is nevertheless probable that the hypertension is renal in origin and that the stimulus to the kidney is the diminished pulse pressure Unfortunately the best evidence that the hypertension of coarctation of the aorta is renal is again experimental It has been shown that artificial "coarctation" of the aorta in an animal only induces hypertension when there is a kidney below the "coarctation," and that the hypertension can be abolished by transplanting the kidney into the neck.

Chronic anæmia provides a good example that a reduced renal

blood flow is an unlikely cause of hypertension, for the renal blood flow may be decreased considerably, yet a raised arterial pressure is most unusual; the pulse pressure in anæmia, however, is much increased.

RENAL HYPERTENSION

The mechanism which causes the blood pressure to rise when there is a primary disease of the kidney is unknown It is attractive to see an analogy with experimental renal hypertension, and in some conditions, e g renal polyarteritis or chronic pyelonephritis, it is possible to show unequivocal occlusive changes in the renal arterial tree. The difficulty about accepting this occlusive theory wholeheartedly is that occasionally severe vascular changes with extensive destruction of the renal parenchyma may be associated with a normal blood pressure. This is seen sometimes in young persons dying with small contracted kidneys, or at any age in renal amyloidosis

VICIOUS CIRCLE HYPERTENSION

The mechanism responsible for this form of hypertension may aggravate every case of hypertension in man, but it is only possible to demonstrate its presence in patients suffering from hypertension and unilateral renal disease In most of these, removal of the diseased kidney does not lower the blood pressure, and it is probable that this is because the hypertension has produced irreversible renal vascular changes in the opposite kidney. This interpretation is quite convincing, for when a unilateral lesion is of short duration the blood pressure often returns to normal following a nephrectomy

It is clear that if there is a strong suggestion that vicious-circle hypertension occurs in unilateral renal disease, it is probable that the same mechanism perpetuates and aggravates hypertension in bilateral renal disease

HYPERTENSIVE VASCULAR DISEASE IN MAN

Hypertension, however caused, is eventually associated with changes in renal structure and function, the structural changes are sometimes known as nephrosclerosis.

Structural Changes

Initially these occur in the vessels but, as the lesions progress, there are secondary ischæmic changes in the nephrons The vascular changes may be either acute or chronic The acute changes consist principally of arteriolar necrosis and are found mainly in association with malignant

hypertension. The chronic changes consist of sclerotic lesions and are found particularly with non-malignant hypertension.

Acute Changes

There is good evidence that the acute arteriolar necroses are a sequel to an intense vasoconstriction of the affected arterioles, and that the vasoconstriction is itself "triggered off" by the elevated blood pressure. This suggests that the principal factor which determines whether the structural lesion is acute or chronic is the response of the arteriole to the elevation in blood pressure, and not the elevation itself. The cause of these differences in arteriolar response to the raised blood pressure is unknown, but malignant hypertension is more common when hypertension is due to renal disease, especially chronic pyelonephritis The proneness of the arterioles to acute lesions is influenced both by the height of the blood pressure and its rate of increase.

The acute vascular changes of malignant hypertension rapidly cause death from renal failure, cardiac failure, or cerebral oedema and hæmorrhage The lesion in the wall of the arteriole consists of (1) localised areas of necrosis of its whole thickness and circumference, and (2) generalised thickening In the kidney these lesions produce acute interstitial hæmorrhage and ischæmic glomerular lesions, with at first a thickening of the glomerular capillary walls and then glomerular atrophy with collagen replacement Initially the glomeruli also show focal areas of acute necrosis which can be recognised as collections of structureless eosin staining material containing isolated disintegrating nuclei and narrow capillary lumens.

Chronic Changes

The chronic vascular changes may occur both with or without hypertension, and consist of a generalised narrowing of the arterioles and intralobular arteries by intimal thickening and accumulation of a homogenous material which stains pink with eosin, a combination of changes known as arteriosclerosis. The lumen eventually becomes blocked, and ischæmia of increasing severity develops. This process may, of course, develop in previously normal kidneys, and may occasionally be severe enough to cause renal failure ; but it also complicates most longstanding cases of renal disease, when it then contributes to, and accelerates, the kidney's eventual destruction In the larger arteries these chronic vascular lesions eventually cause focal wedge-shaped areas of degeneration situated between relatively normal renal tissue. In the affected areas the glomeruli tend to be crowded together. The glomerular tufts show a diffuse thickening with collagen accompanied by a similar thickening of the glomerular capsule ;

eventually the collagenised tuft and capsule become fused, the capillary lumens are obliterated and the glomerulus is replaced by fibrous tissue. At first, the tubules between these glomeruli lose their lumens, but the cells show little change so that the glomeruli appear to be packed in solid wedges of relatively normal cells Later the cells atrophy and there is fibrous tissue replacement When these vascular changes are far advanced there may be no normal tissue left and it may then be impossible, histologically, to distinguish them from the end stages of such chronic renal diseases as glomerular nephritis or pyelonephritis, in which vascular changes are only a complication

Functional Changes

Essential hypertension initially causes little disturbance in renal function ; renal blood flow measurements show renal vasoconstriction with a normal rate of flow, while complex and speculative calculations suggest that the efferent glomerular arteriole constricts to a greater extent than the afferent, and that this is one of the reasons why glomerular filtration rate also remains unchanged Renal biopsies at this time show no abnormality of structure Gradually renal blood flow and glomerular filtration decrease, the latter always to a lesser extent than the former , small amounts of protein appear in the urine [illegible]

[illegible] it is unusual for these changes to become sufficiently extensive to cause symptomatic renal failure With malignant hypertension proteinuria increases and the urine contains many red cells and granular casts , tubular capacity to concentrate is lost , renal blood flow and glomerular filtration rate fall precipitously, and renal failure rapidly develops. If the blood pressure can be lowered without immediately aggravating the renal failure most of the acute structural and functional changes disappear

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10

THE KIDNEY AND OEDEMA

NORMAL CONTROL OF THE VOLUME AND CONCENTRATION OF BODY FLUIDS

WATER is added to body fluids principally by oral intake, but there is also a small contribution of 200–300 ml a day which is an end product of metabolism Water is lost via the skin, lungs and kidneys, loss from the gut is negligible unless there is vomiting, diarrhœa or a fistula The intake of water is controlled by thirst, while its output is adjusted by the kidneys, the amount of water lost from the skin and respiratory tract is mainly dependent on atmospheric conditions and is thus beyond the body's internal authority

Thirst

The sensation of thirst appears to originate in the hypothalamus, it is influenced by a wide variety of factors, the two most important being the osmolarity of the extracellular fluid, and the blood volume. The first can easily be demonstrated by administering hypertonic saline, and the second by performing a substantial venesection. It is probable that the thirst centre is directly stimulated by changes in osmolarity, but it is not known how it is aware of changes in blood volume.

Renal Control of Extracellular Fluid Tonicity

The control of water output by the kidney is intimately connected with the control of sodium chloride excretion, both varying with the need to keep the tonicity of body fluids and the blood volume within normal limits It is probable that the osmolarity of the intra- and extracellular fluids is in equilibrium, so that it is possible for the kidney to maintain tonicity of body fluids simply by adjusting the osmolarity of the extracellular fluid Theoretically this could be achieved by altering the urinary excretion of either water or salt, but in practice it is done mainly by altering the excretion of water. The neurohypophysis responds to changes in plasma osmolarity by rapid alterations in the rate at which the antidiuretic hormone (ADH) is secreted into the circulation, and ADH in turn controls the concentration of

the urine and therefore, the volume of urine that is excreted. For instance a drink of water lowers plasma osmolarity, this inhibits ADH production by the neurohypophysis and within 20–30 minutes the urine becomes hypotonic, whereas with fluid deprivation and a rise in plasma osmolarity the mechanism is reversed

Renal Control of Blood Volume

Changes in blood volume induce alterations in both sodium and water excretion (Fig. 35). It is clear that if the tonicity of body fluids is to remain constant, the ratio of salt to water released or retained must be in isotonic proportions. This synchronisation of the different mechanisms which control salt and water excretion can be demonstrated by bleeding a normal subject, when there is a prompt and simultaneous *decrease* in both salt and water excretion ; or, conversely, by administering blood or a " plasma expander " such as dextran when there is a simultaneous *increase* in salt and water excretion.

The efferent mechanism responsible for changes in water excretion consists mainly in altering hypophyseal function ; those mechanisms responsible for the changes in salt excretion are more obscure. There is now some evidence that in man acute changes are probably produced not only by changes in glomerular filtration rate but also by the renal nerves, perhaps acting directly on the cells of the tubules, while the more prolonged effects are the result of changes in aldosterone excretion and other unknown factors

The afferent pathways are not known It is generally considered that changes in blood volume alter the pulse pressure in some local vascular compartment from the walls of which afferent impulses travel centrally. The site of this vascular compartment has not been determined, but there is good evidence that its area is localised, for it has been found that a change in the distribution of blood, rather than its total volume, is the operative stimulus For instance, standing still induces a pooling of blood in the legs and diminishes the amount elsewhere ; it does not of course change the total blood volume. Nevertheless, the reflex pathways for the control of blood volume are stimulated as if blood had indeed been lost, and there is a decrease in salt and water excretion ; if the legs are first bandaged to prevent pooling, however, standing will not disturb salt and water excretion.

To control the excretion of ADH the afferent impulses need only travel directly to the neurohypophysis The position of the centre responsible for sodium excretion is not known. Contrary to initial expectations it has been shown that the anterior pituitary is not the chief factor in controlling the adrenals' production of aldosterone. It is probable that the " sodium centre " is situated in the hypothalamus,

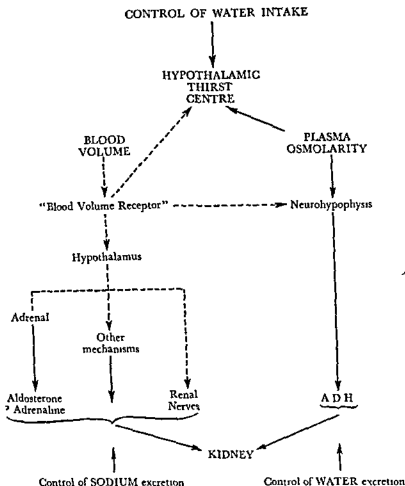


FIG 35 Diagram illustrating the mechanisms concerned in the control of salt and water excretion in response to changes in blood volume and plasma osmolarity Interrupted line indicates uncertain pathways

from which efferent impulses emerge to influence the adrenal, the renal nerves and those other, as yet unidentified, mechanisms which control salt excretion

GENERALISED OEDEMA

It is established that generalised oedema in man is always associated with excessive retention of salt and water by the kidneys. This has

been shown in cardiac failure, malnutrition, the nephrotic syndrome and chronic liver failure. It seems that salt and water retention in all these conditions is due, in part at least, to the same mechanisms which cause a decreased salt and water excretion when the blood volume is reduced. There is a reduction in blood volume with malnutrition, the nephrotic syndrome and chronic liver failure In cardiac failure, however, the blood volume is usually greater than normal and some other afferent stimulus must be involved. It does not appear to be anoxæmia or raised venous pressure The most likely hypothesis, for which there is as yet little evidence, is that when the heart fails, an increased number of impulses come from afferent fibres situated in the myocardium and that these come from alterations in pulse pressure within the chambers of the heart. It is suggested that these impulses then travel to the same centre in the central nervous system which controls salt and water excretion in response to changes in blood volume A high urinary excretion of aldosterone has been demonstrated in the nephrotic syndrome, cardiac failure and chronic liver failure. Nevertheless, there is evidence that in these conditions other unidentified salt-retaining mechanisms are also active.

In the three conditions in which there is a negative protein balance, i e malnutrition, the nephrotic syndrome and chronic liver failure, the reduction in blood volume is due to the diminution in the total number of plasma protein molecules, as less water can then be retained within the vascular compartment. It follows that even if the volume of extra cellular fluid remains unchanged a greater proportion will lie in the interstitial space. If, at the same time, the concentration of plasma proteins falls (which it usually does) and the plasma protein osmotic pressure is reduced, there is an increased filtration at all capillary surfaces and the partitioning of water and salt between the interstitial fluid and the vascular compartment is again disturbed so that there is an increase in the volume of interstitial fluid When the volume of interstitial fluid reaches a certain level it becomes clinically evident as oedema. Fig 36 illustrates the ætiology and probable mechanism responsible for generalised oedema.

It is necessary to mention that many patients suffering from generalised oedema have a reduced renal blood flow and glomerular filtration rate, and at one time it was suggested that the diminished salt excretion was directly related to the decreased filtration rate. This hypothesis was consistent with much animal work, particularly in dogs, in which it seems beyond doubt that acute changes in filtration rate are responsible for striking changes in salt excretion. But it is now clear that prolonged changes in glomerular filtration rate, such as are found in clinical conditions, are of no great consequence to the

excretion of electrolytes. For instance, the removal of one kidney is followed by a normal electrolyte balance, although the filtration rate, in spite of compensatory hypertrophy of the remaining kidney, remains lower than before. Patients with cardiac failure have been observed

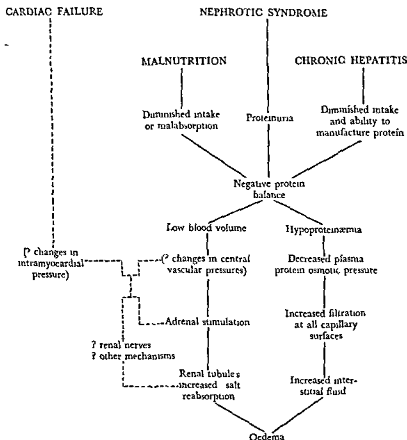


Fig 36 The ætiology and some of the mechanisms responsible for generalized oedema

to have a diuresis of salt and water before any change is apparent in the renal blood flow or filtration rate, and a similar dissociation has been reported in cases recovering from acute nephritis Again, patients with advanced renal disease frequently have a filtration rate which is less than 20 ml per min and may yet be in normal salt and water balance.

Clinical Picture

The incidence of the nephrotic syndrome in relation to age and sex depends largely on its ætiology. The cases can be divided into those in whom the renal lesion is primary and those in whom it is only a feature in a more generalised disease. The primary lesions are more common in men and the majority occur under the age of 60; whereas when the lesion is a feature in a generalised disease the patients are equally distributed between the sexes.

Whatever the cause of the nephrotic syndrome the onset of *oedema* is usually gradual and fluctuating. At first there is occasional swelling of the ankles in the evening, or of the face in the morning There may be transient attacks of more obvious oedema which rapidly disappears

Eventually, after an interval of weeks or months, oedema persists and recovery from each exacerbation is less complete. When the condition is advanced the accumulation of fluid appears to be controlled only by the skin's limited ability to stretch. The legs and arms are unsightly lobulated balloons, shiny and pale ; the abdomen protrudes both with oedema of the subcutaneous tissues and ascites ; the face is spherical, bloated and disfigured particularly by circumorbital oedema, the eyes becoming pink pustular horizontal slits between distended eyelids. Pleural effusions are present, and oedema of the scrotum or vulva may produce huge swellings The oedema is always soft and pits easily with little pressure.

As the oedema appears there is an increasing feeling of lethargy and weakness; and when there are pleural effusions there is dyspnœa. Headache is common and, for reasons which are not understood, patients with the nephrotic syndrome frequently have recurrent " colds " which, though they rarely mature beyond a sore throat and transient nasal obstruction, often cause an acute exacerbation of oedema and proteinuria. Bacterial infections also occur frequently and affect principally the skin, the lungs and the peritoneum When ascites is present there may be sudden attacks of abdominal pain simulating bacterial peritonitis, but laparotomy shows only a few strands of fibrin and sterile fluid; the pain settles gradually after operation Anorexia and diarrhœa frequently occur and, although oedema of the stomach and intestinal mucosa may be partly responsible for both, it is clear that the anorexia is also due to the state of advanced malnutrition. The latter is probably also the cause of (1) the lowered basal metabolic rate, for the thyroid gland function has been found to be normal, and (2) the occasional presence of anæmia in the absence of renal failure.

Hypoproteinæmia is due to a fall in the albumin fraction, and albumin concentrations below 1 g. per cent. are sometimes seen The concentrations of the globulins, however, are liable to increase (except for gamma globulin) and, if only total proteins are estimated, may disguise the severity of the decrease in albumin concentration. Nevertheless because the globulin molecules are larger and heavier than those of albumin the plasma protein osmotic pressure falls There is a rough correlation between the appearance of oedema and the plasma albumin concentration, the dividing line being about 2·5–3 0 g per cent

Hypercholesterolæmia is usually of the order of 400–600 mg per cent. although concentrations above 1,000 mg per cent have been recorded During remissions of oedema or following complete recovery, even when the plasma protein concentrations have returned to normal, blood cholesterol values may remain raised for a matter of months, and only slowly return to normal.

Proteinuria usually exceeds 5 g per day and characteristically fluctuates widely from day to day, being particularly sensitive to posture and exercise ; daily excretions of up to 60 g are sometimes seen, but the usual rate is about 10–15 g per day, it is independent of the rate of urine flow. The daily urine volume obviously depends on whether oedema is forming, remaining unchanged or being evacuated. With low volumes and normal renal function urine concentrations of S G 1·030 are attained. Glycosuria is often found, and microscopy shows the presence of fatty casts and doubly refractile lipid bodies

Diagnosis

The fact that a patient is suffering from a nephrotic syndrome is easy to observe , its cause may be more difficult to ascertain It is suspected from the attendant circumstances and some help can be obtained from renal biopsy Often the correct diagnosis is only obtained in retrospect or at autopsy.

Prognosis

The course of the nephrotic syndrome largely depends on its cause , it varies from complete recovery to death from renal failure , it may last only a few weeks or, with remissions and relapses, up to 20 years. In general, the prognosis is better in women than it is in men, and in the young rather than the elderly. Remissions of oedema may occur at any time and may last several months, with persistent proteinuria as the only evidence of disease Sometimes such a remission may appear complete, with no protein in the urine and yet relapse takes place several years later Renal failure, hypertensive cardiac failure with malignant hypertension and intercurrent infections are the usual causes

of death. There may be periods of transient hypertension and microscopical hæmaturia, but these signs, unless they are persistent or severe, do not necessarily imply advancing destruction of the renal parenchyma. Conversely, gradual structural obliteration may take place without proteinuria diminishing. Renal biopsy can often give some help in prognosis other than by establishing the diagnosis, for it seems that the prognosis may be gauged to some extent by the severity of glomerular change

Treatment

The many varieties of treatment of the nephrotic syndrome are illustrated in Fig. 37. The conditions which give rise to the syndrome are listed at the top and the sequence of disturbed physiology which follows is shown below; the aim of the treatment can be looked upon as cutting across a chain of events at different levels.

Treatment of the Initiating Condition

The successful eradification of the initiating cause of the nephrotic syndrome is clearly the most desirable form of treatment. Cessation of troxidone administration, or the surgical removal of a septic focus, which is giving rise to renal amyloidosis, are two examples. Unfortunately, the primary cause of the nephrotic syndrome is seldom amenable to treatment, and usually therapy has to be aimed at a lower or more symptomatic level Such symptomatic treatment, however, is occasionally followed by a long, lasting remission or even complete recovery.

Treatment of the Proteinuria and Increased Aldosterone Excretion

Frequently the administration of (1) ACTH, (2) adrenal steroids (cortisone and prednisone), or the intervention of (3) an acute attack of *malaria or measles cause a rapid diminution in proteinuria* and aldosterone excretion, and there is a large diuresis and loss of oedema. It is generally considered that the beneficial effects of all three forms of treatment are due to a temporary increase in the quantity of circulating adrenal steroids Presumably the diminution in proteinuria that takes place is due to some alteration in glomerular permeability, and the decrease in aldosterone excretion to inhibition of adrenal function.

Both ACTH and adrenal steroids can be given in large doses over a few days, or adrenal steroids can be given in small amounts for months or years.

Short Intensive Courses of ACTH or Adrenal Steroids. ACTH is given in doses of 40–80 units per day (in the gel form), cortisone 200–

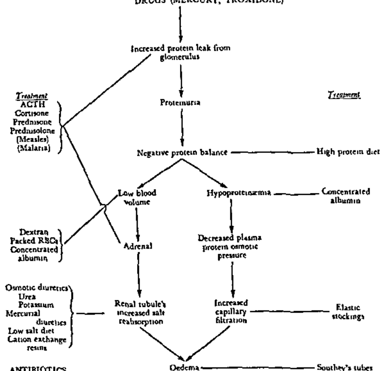


FIG 37 Diseases in which the nephrotic syndrome develops, its *pathological physiology and treatment*

400 mg per day, and prednisone or prednisolone 40–100 mg per day, for courses lasting 10–14 days Of these four, ACTH has been used

2–4 days *following* the end of treatment. Depending on the size of the diuresis, weight loss may be 5–10 lb. a day and is often associated not

only with decreased proteinuria and aldosterone excretion, but also with a rise in glomerular filtration rate. If there is no change in proteinuria or glomerular filtration rate, the diuresis is unlikely to be very great or to give anything but a transient reduction in the oedema. The duration of remissions is variable and is longest when a pronounced initial fall in proteinuria is well sustained. When prednisone produces a remission, a diuresis begins and proteinuria often disappears within the first few days of treatment Remissions of several months are not infrequent and occasionally there is complete recovery. If no diuresis is obtained another course is usually given after an interval of one to two weeks The number of courses which it is considered worthwhile to give in order to obtain a diuresis is not well defined, though some authorities would certainly give at least three.

Such intensive courses may cause the following complications During the first few days there may be oliguria, increased accumulation of oedema, a rising blood pressure, and a rising blood urea These are rarely of sufficient severity to cause any concern, but the urine volume, blood pressure, weight and jugular venous pressure should nevertheless be observed each day, if oliguria develops, or there is an antecedent depression in glomerular filtration rate, frequent blood urea estimations should also be made Infections are also more likely to occur, and they should be treated promptly or anticipated, sometimes antibiotics are given prophylactically during treatment. Acute perforation or hæmorrhage from a peptic ulcer, an acute psychosis or a reactivation of an old tuberculous lesion also occasionally occur.

It follows that the contraindications to ACTH and cortisone therapy are cardiac failure, severe hypertension and advanced renal failure; dyspnoea from large pleural effusions is another contraindication. Because of these difficulties it is probable that in future prednisone will be increasingly used, for such reports as have already appeared, and my own experience confirms that during its administration there is usually less gain in weight or rise in blood pressure, and that the chances of a good diuresis occurring are as great, if not greater, than with ACTH or other adrenal steroids. Prednisone and particularly prednisolone is occasionally effective when both ACTH and cortisone have failed.

If there is a diuresis, there may be other complications such as

feature seen at all frequently is a feeling of faintness and dizziness if the patient is up and about during a particularly extensive diuresis

Prolonged Courses of Adrenal Steroids Long-term administration

of adrenal steroids usually follows after a short intensi
(Fig 38).

Following the initial high dosage the amount of adren
being administered is gradually decreased at about weekly
until cortisone 50–100 mg /day or prednisone 10–20 mg./day
given. In children prednisolone is being used to an increasi



Fig 38 Treatment of the nephrotic syndrome with prolonged c
adrenal steroid The effect of prednisolone in a child Note th
weight *during* the administration of very large amounts of pred
and the early decrease inproteinuria.

beginning with exceedingly large amounts (Fig 38) Co
of prolonged administration are rare, though with higher
porosis, glycosuria and, with cortisone, potassium deficiency
reported These complications are avoided by using
mentioned above and by a high protein, high calorie diet
large quantities of calcium

Finally, the fact that nephrotic children frequently have a remission of oedema *following an accidental attack of measles has occasionally* led to their being exposed to infection deliberately. The results do not seem to be any better than with adrenal steroids, and the treatment is certainly far less pleasant for the child. In adults malaria has been used instead, and similar conclusions have been reached.

Treatment of the Negative Protein Balance

It is imperative that the negative protein balance should be corrected, and the necessity for a high protein diet cannot be overemphasised

The only limit to positive nitrogen balance that can be achieved by these patients is their own capacity for protein ingestion It has been demonstrated that the rate of proteinuria is not affected by high intakes of protein and there is no evidence that renal function suffers in any way, though in patients with an initially depressed glomerular filtration rate it is important to watch the blood urea. A rising blood urea in these circumstances is, of course, no evidence of a further depression in filtration rate but, although a moderate rise to 40–60 mg. per cent. is permissible, higher concentrations may be associated with symptoms of waste product retention and should be avoided. Adults should, and can, eat 150–200 g. of protein a day, which is not difficult if protein concentrates such as Casilan are used and salt restriction is not too severe (see below) At first anorexia is very frequent, but can often be abolished by ACTH, cortisone or prednisone, even if these fail to produce any other immediate benefit. It has been shown that such a diet, continued for several months, and accompanied by a large accumulating nitrogen balance may at first produce no change in plasma protein concentration or oedema, although the plasma volume is gradually increasing. Eventually, when the plasma volume reaches a critical value, the oedema may rapidly recede whether or not plasma protein concentration has altered—additional evidence that the nephrotic syndrome is more closely related to blood volume changes than to plasma protein osmotic pressure.

Treatment of the Low Blood Volume

This link in the causation of the oedema in the nephrotic syndrome can be treated directly by the intravenous administration of concentrated albumin, dextran or packed red cells. Albumin is rarely given, for it is expensive to prepare and has little advantage over the other two. Dextran is used most frequently. It should be salt-free and have either the same or twice the osmotic pressure of normal plasma protein

(5 per cent. or 10 per cent. solutions). The amount given is empirical, but for an adult one litre of the 5 per cent. solution (or 500 ml of the 10 per cent) is sufficient to produce a diuresis in many patients. Packed red cells are sometimes used ; these should increase the blood volume for a longer period than dextran, but it is doubtful whether this is so, for an increase in the red cell mass tends to be associated with a shrinking plasma volume In addition the nephrotic's liability to pyrexial reactions is a serious disadvantage of red cell infusions, unless the cells are washed with 5 per cent. glucose.

Blood volume expanders frequently produce a good diuresis, but shortly after there is usually a period of relative oliguria and a rapid reaccumulation of oedema

Treatment of the Renal Tubule's Increased Salt Reabsorption

Salt and water retention can be minimised by decreasing the salt intake, or increasing the excretion of fæcal sodium by giving cation exchange resins, or it may be directly countered by increasing the urinary excretion of sodium with mercurial or osmotic diuretics

Dietary Salt Content. The amount of salt in the diet should be related to the severity of the oedema. In many long-standing cases of the nephrotic syndrome, in whom proteinuria and oedema fluctuate slowly over a period of months, the dietary salt can be adjusted according to the weight chart. Whereas at one time the patient can eat 5 g of salt per day without putting on weight, a few months later the weight can only be prevented from rising by reducing the intake to 1–2 g When oedema is increasing rapidly it may be imperative to give a " salt-free " diet .The ideal is to give as much salt as the patient can easily excrete , it is often an unnecessary burden to give less and it increases the difficulties of maintaining a high protein diet.

Resins. The difficulties of giving a diet low in salt and yet high in protein can be overcome to a certain extent by the administration of low-sodium protein preparations such as Casilan, and the use of ion exchange resins A cation resin (Katonium, B D.H.), 75 per cent in the ammonium phase and 25 per cent. in the potassium phase, is given orally 15 g four times a day, for an adult In the small intestine the ammonium and potassium on the resin are exchanged for an equivalent amount of the patient's sodium , but much of this sodium is again exchanged for potassium in the large bowel The nett result is a negative balance of sodium and potassium, and the production of an acidosis from the absorption of ammonium (p 49) .The negative sodium balance is the aim of the treatment ; the negative potassium balance and acidosis are complications to avoid The potassium loss can

be countered by the oral administration of potassium citrate 3 g per day *The kidney should be able to prevent the tendency to develop an* acidosis by increasing the excretion of ammonia and free hydrogen ions (p 45), if it is not able to do this adequately an increasing acidosis develops, together with an unexplained decrease in glomerular filtration rate and a rise in blood urea. To avoid these complications the resin is *given intermittently,* e.g on five days a week Its administration should be stopped if the blood urea rises to approximately 75 mg per cent. or the plasma bicarbonate falls to 15 mEq./l. It is clear that resins should not be given to patients who already have a reduced glomerular filtration rate or acidosis When oedema is controlled, but heavy proteinuria continues, it is best to continue resin administration; on occasion the loss of oedema is associated with diminution or disappearance of proteinuria, a rise in glomerular filtration rate, and a return of plasma proteins to normal.

Diuretics *Mercurial diuretics* are rarely advocated in the treatment of the nephrotic syndrome except as an extreme measure, but they are nevertheless widely used They are after all, cytoplasmic poisons, and if it is confirmed that in patients suffering from chronic heart failure the prolonged use of mercurials occasionally causes a nephrotic syndrome, it is unlikely that this cautious attitude will be relaxed. Nevertheless, the parenteral use of mercurials twice a week often produces an excellent diuresis when all other methods have failed, and it has never yet been shown to cause a deterioration in the patient's condition

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be any more successful, and conversely, however effective they have been, it is probably unwise to continue treatment for longer than a month unless the interval between injections can be increased to 10–14 days The best use of mercurials is to produce a rapid and substantial diuresis, often this will cause a welcome, but only transient relief of oedema, at other times though the oedema returns, it is now more easily controlled by other means; and occasionally the oedema disappears and does not return

Osmotic Diuretics. At one time osmotic diuretics had a considerable vogue and the oral administration of potassium salts or urea were in common use. Both have to be given over a considerable time and in large amounts to have any material effect on the urine flow In the case of urea such big doses may lead to nausea, diarrhœa and headaches (p 313), while the administration of large amounts of potassium salts may occasionally give rise to potassium retention and a rising plasma potassium.

Treatment of the Increased Capillary Filtration and Local Oedema

The increase in capillary filtration which takes place at all capillary surfaces as a result of the decreased plasma protein osmotic pressure can be minimised below the knees by wearing elastic stockings In some subjects, particularly young women who have a relatively well controlled nephrotic syndrome, such a measure may enable them to go out in the evening without looking too conspicuous

Oedema fluid can be removed directly by the subcutaneous introduction of Southey's tubes, or by making multiple superficial skin incisions in the legs through an antibiotic cream such as Neomycin If the patient is then kept in a sitting posture large quantities of fluid may be removed, but it is a remarkable fact that occasionally these procedures are unsuccessful for the first few days , then losses of 1–2 litres a day may occur through the same sites and tubes. This initial delay is most often seen when the accumulation of oedema has been so rapid and extensive that the legs are tense, hard and almost impossible to pit upon pressure The danger of secondary infection of the skin during these manœuvres is considerable and prophylactic antibiotics should be given. For some unknown reason, if a large quantity of fluid is successfully removed in this way it may sometimes initiate the onset of a large diuresis.

If ascites and pleural effusions are causing discomfort the fluid may be removed with a needle and syringe, but otherwise this should be avoided for the protein content of such fluid is sometimes relatively high, and its removal diminishes the already depleted protein stores.

Treatment of the Infections

Though the use of antibiotics does not counteract a specific link in the ætiology of nephrotic oedema, their introduction in recent years has nevertheless been the main factor responsible for the longer survival of patients suffering from the nephrotic syndrome. Such patients seem particularly liable to develop infections, and in turn the infections seem to be more severe and are nearly always associated with an acute exacerbation of the nephrotic syndrome. In order to avoid infections oral penicillin is sometimes given daily as a prophylactic ; alternatively the patient is given a short course of a wide-spectrum antibiotic (e g. tetracycline) to take home, to be used at the first sign of an infection

Synopsis of Treatment

Treatment should be started with a low salt, high protein diet, and followed by prednisone or prednisolone. If a quick evacuation of the

oedema is required because the adrenal steroids have not produced a diuresis and the patient is uncomfortable, a large oral dose of ammonium chloride and an intramuscular injection of a mercurial diuretic may be given at the same time as a rapid intravenous infusion of one litre of 10 per cent. Dextran. The diuretic effect of these manœuvres is greater if they are performed two to three days after the temporary withdrawal of adrenal steroid therapy. Such a three-pronged simultaneous approach is sometimes successful when each method used singly has been unavailing

Ion exchange resins can also be given either as an alternative, or in conjunction with steroids. Antibiotics should be given at the first sign of infection, or as a daily prophylactic dose.

If the oedema is painful or incapacitating, even with the patient in bed, its removal can be attempted by subcutaneous tubes or multiple skin incisions, and this should be done under cover of antibiotics

A high protein diet and the administration of ion exchange resins cannot be used when there is evidence of renal failure.

In order to be aware of the progress of events it is useful to insist on the following being measured and recorded once a day: (1) Body weight; (2) blood pressure; (3) fluid intake and output excluding food and fæces; (4) 24-hour urinary protein excretion; it is also useful to measure the blood urea and creatinine clearance at regular intervals of one to two weeks, and the plasma proteins at least once a fortnight.

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12

ACUTE RENAL FAILURE

ACUTE renal failure can be arbitrarily defined as any condition in which the daily volume of urine passed into the bladder is suddenly reduced below 400 ml. This definition inevitably includes severe but physiologically normal oliguria, which is sometimes called "acute renal insufficiency."

Aetiology

(1) Severe functional changes without structural damage
(2) Severe functional changes with acute structural damage.
(3) Functional changes of perhaps moderate severity but occurring in a patient with chronic structural damage.
(4) Acute urinary tract obstruction.

Severe Functional Changes without Structural Damage

The most important of these changes is severe but initially reversible renal vasoconstriction, the causes of which have been discussed on p 68; they are predominantly those which cause acute circulatory insufficiency Typical examples are the sudden reductions in blood volume which may accompany acute diarrhœa and vomiting, burns and hæmorrhage *The reduced renal blood flow which results is* associated with a reduced glomerular filtration rate and thus a decreased excretion of solutes. Usually there is a simultaneous stimulation of the supra-optico-hypophyseal system and an increase in the level of circulating antidiuretic hormone. The oliguria which results is thus associated with a urine which at first is highly concentrated. Some of the most severe but rapidly reversible oliguric episodes may occur in the first two days after operation when the 24-hour urine volume may be 150 ml.

Severe Functional Changes with Acute Structural Damage

A wide variety of conditions may give rise to acute structural changes severe enough to cause acute renal failure; they are illustrated in Fig. 39. They include severe forms of certain renal diseases which usually present in a less acute form, i.e acute nephritis, acute pyelonephritis with acute necrotising papillitis, malignant hypertension, polyarteritis nodosa and eclampsia. Numerically these are not

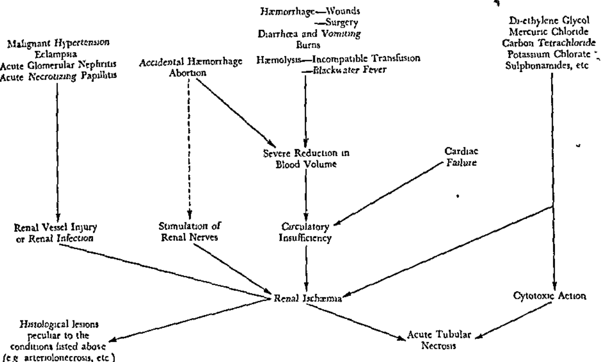


FIG 39 Ætiology of acute renal failure with acute structural changes

important causes of acute renal failure. The most common form of structural damage is acute tubular necrosis. In the past this condition has been called "lower nephron nephrosis," "shock kidney" and "crush syndrome."

Tubular necrosis may follow directly from the action of poisons or severe prolonged renal vasoconstriction. Poisons act directly by causing the death of those tubular cells which transport the substance from the blood into the lumen of the tubule; they also cause intense renal vasoconstriction and irregularly distributed focal patches of renal ischæmia, which in turn become the sites of ischæmic tubular necrosis. Mercury, arsenic, lead, bismuth, carbon tetrachloride, potassium chlorate, propylene glycol and sulphonamides are some of the substances which have been known to cause acute tubular necrosis; for this reason they are called nephrotoxins.

The causes of renal vasoconstriction which may produce tubular necrosis are the same as those which have been discussed above and in Section 8. Necrosis is due to the intensity and duration of renal ischæmia, i.e. it must be present for a matter of hours, a point of immense importance in trying to prevent the condition. Abortion, multiple wounds and extensive surgery with inadequate blood replacement are the most frequent causes of tubular necrosis. Though it is probable that renal vasoconstriction without a concomitant fall in blood pressure may occasionally be sufficiently intense to cause necrosis, it is clear that necrosis is more likely if there is a combination of vasoconstriction and hypotension. It is not always appreciated that the more intense the vasoconstriction the higher the minimal arterial pressure necessary to keep the vessels open This is important clinically, for when there is severe renal vasoconstriction minor falls in blood pressure may be sufficient to cause complete ischæmia

Whether a shunting of blood through the juxtamedullary glomeruli and away from the cortex ever occurs in any of these situations is not open to demonstration. The meagre evidence that has been obtained in man does not support the idea, and observations made on animals suggest that if there is such a diversion, it is of little consequence compared with the severity of the total renal ischæmia with which it is associated.

In acute renal failure with acute structural changes the specific gravity of the urine is approximately 1·010.

Acute Functional Changes Superimposed upon Chronic Structural Damage

Patients suffering from chronic renal failure due to a gradual obliteration of their nephrons may be precipitated into acute renal

failure by some disturbance which, in a normal person, would cause only an insignificant change in renal function This combination of acute functional changes and long-standing structural damage is sometimes very difficult to differentiate from acute structural damage in previously normal kidneys, particularly if the pre-existence of chronic renal disease is unknown. In both, the specific gravity of the urine will be fixed near 1·010 The differential diagnosis is based on obtaining clinical evidence of long-standing renal failure such as a history of polydipsia, polyuria, lassitude, and the presence of pigmentation and anæmia

Acute Urinary Tract Obstruction

Bilateral pelvic or ureteric obstruction, or unilateral obstruction to a single functioning kidney can obviously cause acute renal failure This indisputable truth is often forgotten when considering the differential diagnosis of acute renal failure. Pus, clots of blood, crystalluria and tubular débris can cause acute bilateral obstruction There is also a rare condition known as calculus anuria when acute bilateral anuria results from the presence of a calculus in only one ureter

The outstanding feature of the acute renal failure due to acute urinary tract obstruction is that the flow of urine is completely suppressed, as opposed to the low flows which are usually found with acute structural damage to the renal parenchyma The only exception to this rule is in the acute renal failure of acute glomerular nephritis The therapeutic implication of this fact is that if acute renal failure is associated with complete or almost complete suppression of urine, a cystoscopy should be performed and the ureters catheterised to try to relieve the obstruction , if this is unsuccessful it is necessary to release the urine above the obstruction by a nephrostomy

TUBULAR NECROSIS

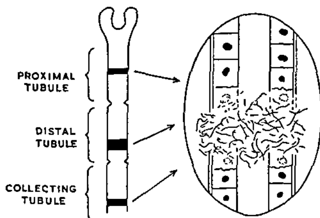
The following sections describe the pathological findings, clinical features, treatment and prognosis in acute tubular necrosis. The clinical features and treatment of acute renal failure due to other causes are almost identical.

Pathology of Acute Tubular Necrosis

Macroscopically the kidneys do not look greatly disturbed and may often be passed as normal When the kidney is incised there is a tendency for the cortex to bulge and to look slightly pale. The only unmistakable macroscopical appearances are those associated with extensive necrosis such as are found with eclampsia and accidental

hæmorrhage (p. 262) when the condition is called acute cortical necrosis.

Microscopically the lesions are most clearly displayed in nephrons which have been microdissected. By this technique it has been possible to show that there are two distinct lesions ; one is due to ischæmia and occurs in a random distribution throughout all nephrons and in any part of the nephron down to the collecting tubule ; the other, which is due to nephrotoxins, affects all nephrons equally, and is confined to the same part of each *proximal* tubule. Each ischæmic lesion involves only a relatively short length of the nephron



ISCHAEMIC LESION OF

TUBULAR NECROSIS

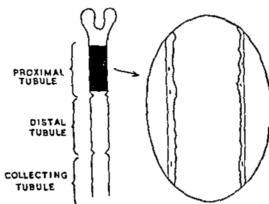
FIG. 40

and consists of complete necrosis of the tubule cells and the basement membrane, thus exposing the lumen of the tubule to the renal interstitial space (Fig. 40). The nephrotoxic lesion involves a considerable segment of each proximal tubule and consists of necrosis of tubule cells only, without involvement of basement membrane (Fig. 41). Nephrotoxins, however, not only cause the death of those tubule cells which transport them, but in addition their presence in high concentrations causes intense renal vasoconstriction. In acute tubular necrosis from nephrotoxins, therefore, both ischæmic and cytotoxic lesions are found

These findings should dispose once and for all of the term " lower nephron nephrosis " : the condition is clearly not confined to the

"lower nephron" nor has it any connection with the appearances found in the kidneys of patients who have suffered from a nephrotic syndrome.

Ordinary histological sections of the kidney show that the glomeruli escape injury while the even distribution of the nephrotoxic tubular lesions are easily recognised, the ischæmic lesions, however, are much more widely spaced and may not be present in a renal biopsy. There are a few foci of round cell infiltration and occasionally some of the tubules are surrounded by a clear "halo"-like area which is thought to be evidence of interstitial oedema Numerous hæmecasts are seen



NEPHROTOXIC LESION OF TUBULAR NECROSIS

FIG 41

in those cases which follow an incompatible blood transfusion or widespread muscle injury

Clinical and Biochemical Features of Acute Tubular Necrosis

Following the particular episode which has precipitated tubular necrosis and which may be defined as the onset, the natural history of the disorder can be divided into three phases :

(a) The oliguric
(b) The diuretic.
(c) The postdiuretic

Oliguric Phase

The early part of the oliguric phase is frequently unrecognised, for it often begins during a surgical or medical emergency. In this setting, the fact that the kidneys have almost ceased to function may not immediately alarm, so great is the relief that the patient is still alive. The daily volume of urine excreted varies, but complete cessation of urine flow does not occur with tubular necrosis. At least 50–100 ml. is excreted daily; it is often dark and discoloured by breakdown products of blood, and at first may be thickened by the débris of necrosed tubular cells, yet the specific gravity of this small volume of "concentrated"-looking urine is always around 1·010, a paradox which confirms the diagnosis

During the oliguric phase the renal blood flow is greatly reduced, but the cause of this continuing renal ischæmia is not known It persists for many days after the situation which precipitated the initial renal ischæmia of the onset has been corrected. It has been suggested that renal ischæmia continues because the intrarenal pressure is raised, for straight X-rays of the abdomen show the kidneys to be much larger than normal. This hypothesis, however, is no longer tenable, for the intrarenal pressure has been measured and found to be normal. Neither does the persistence of the renal ischæmia appear to be due to a maintained nervous vasoconstriction. The most likely explanation is that the initial ischæmia causes changes in the tubule cells from which vasoconstricting metabolites subsequently diffuse and maintain the ischæmia.

Associated with the ischæmia there is a gross reduction in glomerular filtration rate and severe disturbance of tubular function Urea, creatinine, potassium, phosphate, sulphate and a considerable quantity of unidentifiable anions (which have been aptly called, for want of a better name, "anuric anions") therefore accumulate in the blood and extracellular fluid There is also an accumulation of hydrogen ions with a fall in plasma *p*H and bicarbonate. The increase in the concentrations of potassium, phosphate and urea are due to their release from the breakdown of muscle protein, and the rate of this release which is greatest during the first few days of the oliguric phase largely determines the course of the illness The danger to life is that the rising concentration of plasma potassium may cause cardiac arrest. This threat is accentuated by the rise in phosphate which lowers the plasma calcium, and, as potassium and calcium ions have opposing actions on heart muscle, the lowered calcium and the raised plasma potassium summate in their ill effects on cardiac function. The rate of protein catabolism is greatest following injury to muscle, hæmor-

rhage and trauma in the young and healthy ; elderly or debilitated

attempt to relieve the oliguria by the administration of large quantities of water ; an intuitive therapy based on the naïve principle that "what goes in must come out." This is a particularly easy trap to fall into for these patients are often excessively thirsty, probably because of the diminished blood volume which so frequently accompanies the onset of tubular necrosis. It has been shown, however, that plasma osmolarity gradually falls even if the water intake is limited to an amount which is normally lost by insensible means At first there was thought to be a shift of sodium into the cells, but it now appears that the most important factor is an increase in the extracellular water. This is derived both from the intake, for the insensible loss of water is below average in these patients, and from "metabolic water" formed by the endogenous breakdown of protein and fat ; a quantity which may amount to 300 ml a day It is important to recognise the origin of this hypotonicity, for its prevention and correction depends on restricting the intake of water, and *not* in administering large quantities of normal or concentrated saline intravenously , this only expands the extracellular fluid space and may lead to cardiac failure

Other changes evident in the blood are the development of anæmia and a leucocytosis. The anæmia develops rapidly, fails to progress beyond a certain severity though the oliguria may continue, and often becomes more pronounced when the blood urea concentration is beginning to fall The cause of the anæmia appears to be a combination of bone marrow depression and hæmolysis.

These many changes in the internal environment can only be diagnosed with certainty by laboratory estimations . they are associated with the following rather vague clinical signs. The fall in plasma *p*H results in deep regular sighing respirations which are easily recognised, but the other electrolyte changes produce signs which are singularly non-specific, even when they are of sufficient severity to threaten the patient's life. Overhydration causes mental dullness and headache, nausea, vomiting and convulsions. It has also been said to cause psychosis and fever. Expansion of the extracellular fluid space is recognised by a rise in jugular venous pressure, oedema, tachypnœa and pulmonary crepitations. The rise in plasma potassium and the fall in plasma calcium concentrations are stated to be responsible for anxiety, restlessness, paræsthesiæ and hypotension , these are particularly unreliable signs. Serial electrocardiograms are more valuable ;

initially there is "tenting" of T waves with ST segment depression, flattening of the P wave, and a lengthening of the QRS complex so that it resembles bundle branch block; at higher concentrations of potassium the E.C G. takes on the appearance of an untidy sine wave and there may be periods of standstill and irregular rhythm Death occurs from cardiac standstill and ventricular fibrillation In traumatic cases, particularly those with extensive injury to muscle, the rate of rise of plasma potassium to a lethal concentration may be extremely rapid: a concentration of 6–7 mEq./l. rising to 10 mEq /l overnight

Gastro-intestinal disturbances including hiccoughs are frequent during the oliguric phase; their cause is unknown, but they become more severe as the blood urea rises; both vomiting and diarrhœa may occur and they are usually made worse by oral feeding. Occasionally there is hæmatemesis and melæna. As the oliguric phase lengthens there is a gradual clouding of consciousness, nausea and lassitude, fading into a twitching coma. These features seem to be directly due to the retention of some unidentifiable waste products, for they can be relieved by the use of the artificial kidney even if the concentration of blood urea and identifiable electrolytes are left uncorrected.

A rise in blood pressure is infrequent.

It is important to be aware that these patients are very liable to develop infections, it is considered by some that these are now the commonest causes of death

Diuretic Phase

This phase begins when the 24-hour urine volume reaches 1,000 ml. Together with the onset of diuresis the renal blood flow and glomerular filtration rate gradually increase Sometimes, however, the diuresis begins without any marked change occurring in either At first the urine appears to be pure plasma filtrate, for the total concentration of the urine, and of each of its constituents, is identical with that of plasma. As the urine volume increases, the tubules recover some ability to reabsorb salt and concentrate urea so that the urine now contains less salt and more urea than plasma, but the total osmolar concentration still remains about the same as that of plasma, i e. isotonic.

During the first few days of the diuretic phase the patient's general condition changes markedly, there is an increased awareness, nausea and vomiting cease, and appetite returns. The overall improvement is such that when blood urea estimations are found to be either unchanged. or even a little higher than before the onset of diuresis, there is often an atmosphere of disbelief in the accuracy of the estimations Never-

theless this is the recurrent pattern of recovery and is another indication that the symptoms of renal failure are not due to the high concentrations of blood urea. The diuretic phase may be a week old before the blood urea begins to fall

At the height of the diuresis the daily urine volume may be very great (e g 6 1), so that whereas a few days before the patient's life was threatened by an excess of water, salt and potassium, it is now exposed to the perils of dehydration, salt loss and potassium lack The cause of this extensive diuresis appears to be a combination of three mechanisms (1) An osmotic diuresis due to the high blood urea; (2) tubular functional inadequacy, and (3) the release of an accumulated surplus of fluid and electrolytes Obviously if (1) and (2) are responsible for the large diuresis, dangerous electrolyte and water deficiencies may occur, whereas if it is due to (3) it is to the patient's advantage The urine volume rises to a peak and then falls to normal values, the duration of the diuretic phase is roughly the same as that of the oliguric phase

Postdiuretic Phase

This stage develops imperceptibly from the diuretic phase and is characterised by a normal output of urine although there continues to be some impairment of renal function Gradually renal blood flow and glomerular filtration rate increase, and the ability to concentrate the urine, and other tubular functions, return towards normal over a period of about one year Nevertheless, follow-up studies have shown that although renal function is perfectly adequate, full recovery is unusual.

TREATMENT

The first thing to do is to confirm that acute renal failure has indeed taken place, and it is essential to catheterise the bladder to exclude urinary retention The next step is to decide whether the oliguria or anuria is due to urinary tract obstruction, if this is considered probable, or even remotely possible, cystoscopy and ureteric catheterisation should be performed and any obstruction either dislodged, or relieved by nephrostomy.

Acute tubular necrosis and other forms of acute renal failure should be treated along the following lines

Treatment of the Onset

During the onset of acute renal failure, when there is severe renal ischæmia, but before tubular necrosis has occurred, it should be possible (except in the case of poisons) to prevent necrosis by prompt

transfusion, or electrolyte and water replacement, whichever is appropriate It is imperative that transfusions should not be withheld on the grounds that, as the patient is already suffering from acute renal failure, he should not be exposed to the risks of a mismatched transfusion It would be as logical to refrain from throwing a lifebelt to a drowning man for fear it might hit him on the head.

It is wise to try and decide by examining a blood film whether the loss of blood has occurred in an already anæmic person, for if such a patient is transfused so that the hæmatocrit rises above its usual level, renal failure may be aggravated (p. 72), particularly if there is already some degree of chronic renal structural damage.

When acute renal failure follows diarrhœa and vomiting, pyloric stenosis, etc., electrolyte and water losses should be replaced even though the presence of oliguria makes the dangers of overadministration more likely

Ideally the patient should never be allowed to become oligæmic long enough for severe renal ischæmia to develop. If acute renal failure does supervene it is essential that its time of onset should be determined as accurately as possible, for though rapid intravenous therapy may be life-saving in the first few hours, 24–48 hours later it may only precipitate pulmonary oedema, cardiac failure and death

Treatment of the Oliguric Phase

The aim of treatment during the oliguric phase is to keep the internal environment normal until the kidneys recover. It is clear that this aim is limited by two factors: (1) the rate at which the internal environment changes, which is mainly dependent on (*a*) the rate of catabolism, and (*b*) the efficacy of treatment; and (2) the duration of the oliguria. If the internal environment changes relatively slowly, and the oliguria does not last more than two to three weeks, conservative treatment should be sufficient. But if the internal changes are rapid or the oliguria prolonged then it may be necessary to supplement conservative treatment with artificial dialysis. In practice it is the rate of change which is most liable to vary, and this in turn is largely determined by the extent of the associated trauma and infection. When there is no trauma, e g. following abortions and poisoning, the rise in blood urea and potassium is often so gradual that conservative treatment is adequate. But with extensive trauma, e.g gun-shot wounds and road accidents, deterioration is so rapid that artificial dialysis is usually necessary. This dissimilarity is not only due to probable differences in the rate of catabolism but also to the fact that traumatic cases, and particularly war casualties, are liable to have large

quantities of intracellular products released from non-viable muscles which have been overlooked during débridement

Whatever means are employed to treat acute renal failure, plasma electrolytes should be estimated at least once a day; an indwelling catheter should be placed in the bladder, the daily urine volume should be measured and its content of electrolytes estimated. The patient should be weighed each day if at all possible, and a daily weight loss of 0 2–0 5 kg. should be the aim, for this is approximately the weight of endogenous solids which are metabolised each day.

Conservative Treatment

Control of Water Intake. As soon as it is considered that the patient is not deficient in water, the intake of water is limited to between 500 and 700 ml a day, plus a quantity equal to the amount of urine passed in the previous 24 hours The total amount is increased in very hot weather and if there is much sweating. The amount of water required is best gauged by the weight (see above) and the effective plasma osmolarity (i e total osmolarity less the osmolarity due to the urea content); if it is not possible to estimate the plasma osmolarity the concentration of sodium is a less exact but useful substitute. The weight should fall gently while the plasma osmolarity or sodium concentration should not change.

Control of Electrolyte Intake. Following any initial replacement that may be necessary the further ingestion or administration of electrolytes (except for calcium) must be prevented

The plasma concentration of potassium should be kept below 7 mEq./l Some authorities have suggested that this can be done by the intravenous administration of calcium gluconate and insulin (50 units per day) throughout the 24 hours The latter, in association with a high glucose intake (see below), tends to draw the potassium into the cells and so lower plasma potassium. This is certainly true on a short-term basis, but the evidence that it is of much practical value over a prolonged period is not very strong. Resins in the sodium phase can also be used to lower plasma potassium, but their use needs much patience, for the resin is difficult to swallow, the dose is 15 g three to four times a day orally, or 30 g. as a retention enema with promulsin emulsion.

The fall in plasma sodium and chloride should be treated by limiting the fluid intake, for, unless there is a very clear indication of sodium and chloride loss before the onset of renal failure, its administration in order to correct plasma concentrations is potentially dangerous. This also applies to any attempt to correct the acidosis by giving sodium bicarbonate or sodium lactate, for the dangers of expanding the

extracellular fluid volume and causing cardiac failure are greater than any benefit gained by a transient change in *p*H.

Control of Protein, Carbohydrate and Fat Intake. It is obvious that protein should not be given.

Carbohydrates are permissible, as long as they are free of electrolytes They are given principally in the hope that they will slow the rate of endogenous protein breakdown and minimise the rise in plasma potassium concentration (see above). There is good evidence that in normal fasting subjects the daily administration of 100 g. of carbohydrate reduces endogenous protein destruction by about 50 per cent., and that greater amounts have little additional effect It is not at all certain whether these findings are applicable to patients suffering from acute renal failure, and some workers have been unable to produce any convincing change in protein breakdown.

Fats have a similar " protein-sparing " effect and can, theoretically, be used instead of, or in combination with carbohydrates But as they cannot safely be given intravenously, and their administration by stomach tube is apt to cause diarrhœa, they are rarely used

Route of Administration of Water and Carbohydrates

If 100 g of carbohydrate is dissolved in 500–700 ml of water, the concentration of the solution is about 15–20 per cent.; if larger quantities of glucose are thought necessary in order, for instance, to lower the plasma potassium, the solution will have to be even more concentrated As urine flow increases, and the total amount of water that can be given rises, the concentration of the solution can be reduced, which greatly eases its administration. The following remarks are mainly concerned with the difficulties of administering high concentrations of carbohydrate in water.

Stomach. The simplest way to give the required amounts is by mouth as 20 per cent. lactose, it is less sweet and therefore less likely to cause nausea than glucose. If the taste is not tolerated, or greater concentration are considered desirable, 20–50 per cent. glucose can be dripped into the stomach through a small œsophageal polythene tube. But the presence of the tube is apt to induce vomiting, and the higher concentrations of glucose sometimes cause diarrhœa.

It is clear that this route cannot be used if the patient suffers from some surgical condition of the abdomen or is easily nauseated

Peripheral Vein. An isotonic solution of glucose is one of 5 per cent.; if concentrations of 10–15 per cent. are given into a peripheral vein, pain and thromboses are apt to occur after about 6–10 hours. If the patient has many easily accessible veins an attempt can be made

to give a 15 per cent. solution by changing the site of the intravenous needle at about 8-hourly intervals In this way thrombosis may be avoided and a continuous administration maintained. If the veins are "poor" then it is unwise to give a concentration greater than 10 per cent., and even with this concentration the veins are more likely to remain patent if the site of the needle is changed at least once a day. Pain and swelling over the vein can sometimes be controlled by placing 10 mg. of hydrocortisone in approximately each litre of infusing fluid, and clotting in the needle can be prevented by adding 1,000 units heparin.

It is most unusual to be able to give 100 g glucose per day into a peripheral vein at these high concentrations. When difficulties occur the attempt to give glucose is sacrificed to the need to keep the water intake within the bounds described above, and the concentration of the infusions are lowered

Central Vein Glucose concentrations as high as 50 per cent. can be infused intravenously through an indwelling polythene tube placed into the inferior vena cava via a saphenous vein, for the 0 2–0 5 ml. per min of glucose solution is diluted in 2–3 litres of blood This technique needs the least supervision and causes little overt trouble at the site of the infusion, if heparin (1,000 units per litre) is placed in the solution the tube does not become clotted, the rate of flow is always easily controlled and has no sudden fluctuations; the patient has both arms free and is not subject to recurrent needle punctures and tender veins Nevertheless there is one serious complication which makes the use of this method potentially dangerous In a few cases a thrombus forms at the saphenous vein incision and spreads up through the common iliac vein into the inferior vena cava. There have been some fatalities from pulmonary emboli in patients who have recovered from the renal failure This seems a grave risk to run when it is uncertain whether the administration of these large amounts of glucose is of any benefit

Control of Nausea and Vomiting These may sometimes be controlled with chlorpromazine, preferably by injection.

Control of Anæmia. It is usually inadvisable to try to treat the progressive anæmia by transfusions, for the risk of inducing cardiac failure is very great.

Control of Infection The likelihood of infection is so great that some centres now treat all patients with acute renal failure with barrier nursing and prophylactic antibiotic administration. It must be remembered that if the antibiotic that is used is one that is usually eliminated in large amounts in the urine, e g streptomycin, it may be dangerous, after the initial loading dose, to give more than small maintenance doses.

Therapeutic Measures to Avoid

The frustration of seeing a patient gradually dying from acute renal failure, who may have been recently saved from death by an emergency operation, has in the past prompted the use of certain useless and dangerous measures As they are still occasionally used they are enumerated here, so that their eventual eclipse may be hastened.

(1) The intravenous administration of osmotic diuretics ; sodium sulphate is particularly dangerous for it expands the extracellular fluid space and may cause cardiac failure.

(2) The attempt to force a diuresis by overexpansion of the extracellular fluid space with large quantities of intravenous saline; this will almost certainly cause cardiac failure.

(3) Encouraging the patient to drink large quantities of water while giving 5 per cent. glucose intravenously; this causes water intoxication.

(4) Renal decapsulation and paravertebral block ; the trauma of the first procedure hastens the rise in blood urea, while the second may cause hypotension

None of these measures is beneficial; some are lethal.

Artificial Dialysis.

There are three ways of doing this :

(1) Peritoneal dialysis.
(2) Irrigation of the intestine.
(3) Passing the patient's blood through an artificial kidney.

The principle of these techniques is simple, but the difficulties inherent in their use are multiple and complex. It is easy to remove large quantities of excess urea and potassium with any of these methods, but in doing so care must be taken that the patient is not inadvertently depleted of, or flooded by, some other water-soluble substance.

The artificial kidney is by far the most efficient of these techniques, but its safe use necessitates a permanent staff of mechanics, biochemists and doctors. In civilian practice the indications for its use are so infrequent that it is difficult to decide where such machines should profitably be situated Experience has shown that it is invaluable in treating acute renal failure in war casualties.

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and

live

artificial kidney is not available, the most convenient substitute is peritoneal dialysis. A multiholed polythene tube 7–9 inches long is inserted into the lower abdomen via a trocar placed either in the

midline or laterally in one of the iliac fossæ. Two litres of the dialysing solution is run into the peritoneal cavity under gravity and allowed to remain for 10 minutes, when it is then siphoned off and the process repeated with a fresh 2 litres. Ten minutes has been found to be optimum time for the solution to come into equilibrium with the extracellular fluid. The composition of the solution used can be altered according to the requirements of individual cases, but the following is a useful standard solution :

		g/l		mEq /l
	NaCl	6 1	Na	130
	$NaHCO_3$	2·2	K	4 6
	KCl	0 35	Ca	4·2
anhydrous	$CaCl_2$	0·23	Mg	1·1
anhydrous	$MgCl_2$	0 05	Cl	114
	NaH_2PO_4	0 07	HCO_3	26 3
	Glucose	20 00 (i.e. 111 m. osm l.)	H_2PO_4	1 1

Total electrolyte mEq /l. = 281·3
Total m osm. l = 392 3.

The glucose concentration and total osmolarity are high to encourage the transfer of water into the dialysing fluid. Penicillin 100,000 units and tetracycline 25 mg. are added to each litre immediately before being placed into the peritoneum. The number of irrigations depends on the initial level of blood urea and plasma potassium, but about 8 to 16 consecutive irrigations are usually sufficient to produce a well-marked effect The most scrupulous aseptic technique must be maintained, for peritoneal sepsis is the commonest complication of this form of treatment.

Treatment of the Diuretic Phase

It is vital that the strict regimen of the oliguric phase should be continued until the daily urine volume exceeds 1,000 ml , for accumulation of waste products and inability to adjust electrolyte and water balance may still be present at urine volumes below this level. Frequently a partial recovery with a daily urine volume of about 700 ml may progress no further for several days, it is imperative that during this time treatment should not be relaxed

Once the diuretic phase begins the dangers to look out for and correct are water depletion, salt loss and potassium loss It has become clear that much of the polyuria which these patients experience is often only the evacuation of excess extracellular fluid, and attempts to replace it only prolong the diuretic phase and may lead to over-

functioning nephrons It follows, therefore, that each surviving nephron must be handling much larger quantities of solutes and water than normally This is a situation similar to that obtaining in each nephron of a dehydrated normal person who has been given a large quantity of a solute, such as sucrose, mannitol or urea which is then promptly excreted in the urine the rate of solute excreted per nephron increases, and there is a concomitant rise in urine flow and *fall in urine concentration*, i e there is an osmotic diuresis (p 42). An impaired capacity to form a hypertonic urine in chronic renal failure must be partly due to this phenomenon

In chronic renal failure there is thus frequently an increased turnover of water, but paradoxically there is diminished ability to excrete a water load rapidly This occurs before as well as after the ability to make the urine hypotonic has disappeared When it is present before, it is presumably due to the diminished number of nephrons, for even if each nephron forms a hypotonic urine at a normal rate there is an insufficient number to increase the total urine flow adequately This is the reason why polyuria is never gross in chronic renal failure and seldom exceeds 3–4 l /24 hours, in contrast to the 8–10 litres found in diabetes insipidus, or compulsive polydipsia. When the kidneys can no longer form a hypotonic urine the inability to excrete a water load is easier to understand, but the cause of the isosthenuria is not at all clear. It is not consistent with the known facts about osmotic diureses in normal persons (p 42) to attribute an inability to form a hypotonic urine to an osmotic diuresis per nephron ; it seems more likely that it is due to a diminished functional capacity of the surviving nephrons.

These disturbances make patients suffering from chronic renal failure vulnerable to acute changes in water balance. Diarrhœa and vomiting may quickly cause severe dehydration, for the output of water and salt does not drop as sharply as in the normal ; conversely, an impetuous intravenous administration of water (5 per cent. glucose) may cause overhydration Sometimes slight nausea with a distaste for eating and drinking is sufficient to cause dehydration, when a vicious circle of increasing renal failure, more pronounced nausea, and further dehydration then occurs.

Acid Base Balance, Sodium and Potassium Metabolism

On a normal diet the kidney has to excrete about 40 to 60 mEq a day of hydrogen ions to prevent the internal environment from becoming acid (p 45). In chronic renal failure, though the ability to excrete a urine of low *p*H remains normal, the diminished number of nephrons reduces the total capacity of the kidney to excrete hydrogen and ammonium, and there is an increasing acidosis. This is evident as a

fall in plasma pH and bicarbonate The fall in bicarbonate is also due to the retention of phosphate, sulphate and other anions, some of which have not yet been identified

Kussmaul respiration is the only clinical feature which is undoubtedly due to the acidosis, its severity is determined as much by the rate of fall in pH as by the extent of the reduction In addition there is a considerable list of signs and symptoms, particularly of the alimentary and central nervous systems, which it is considered may possibly be caused by the acidosis It is more probable, however, that the pharmacological actions of the unidentified "renal failure anions" are responsible. These clinical disturbances are discussed below

It has been pointed out above that abnormalities of electrolyte balance are unusual until the final stages of chronic renal failure. As the nephron population diminishes each remaining nephron reabsorbs less salt and secretes more potassium This is an adjustment which is not purely passive, for salt reabsorption can be increased by dietary salt restriction or cardiac failure, and potassium excretion may exceed the amount that is filtered A preponderant deficiency, or retention of either sodium or potassium, is therefore unusual, the clinical features of isolated sodium, and potassium deficiencies are dealt with on p. 147.

Calcium Metabolism

There are two main disturbances of calcium metabolism in chronic renal failure (1) An impaired ability to absorb calcium from the bowel which causes a chronic negative calcium balance, and leads to osteomalacia in adults and rickets in children ; and (2) a hyperplasia of the parathyroid gland which gives rise to the bone changes characteristic of hyperparathyroidism, i e osteitis fibrosa Both disturbances are usually present at the same time though one may be more evident than the other

It is not known which particular disturbances in chronic renal failure are responsible for these functional abnormalities in the small bowel and the parathyroids, they only occur in patients whose blood urea has been raised for a considerable time It has been shown that, contrary to first expectations, they are not related to the plasma concentration of phosphorus or the presence of acidosis There is no correlation between the blood levels of calcium and phosphorus and the type of bone lesion, though the majority of patients have a low serum calcium and a raised plasma phosphorus, the alkaline phosphatase level is nearly always raised The impaired ability to absorb calcium is relatively vitamin D resistant but will respond to large amounts

In addition to osteomalacia and osteitis fibrosa there may be focal areas of increased calcium deposition, both in the bones (osteosclerosis)

infrequently the patient retains a complete understanding of what is happening to him right up to a few hours before death.

Epileptic convulsions in chronic renal failure may be due either to sudden increases in blood pressure in patients with established hypertension, or they may occur without any change in blood pressure. Both types are very rare, the first is called hypertensive encephalopathy; the other has no particular designation. The latter variety is seen mainly in young adults in whom the fits may be the only complaint and yet the blood urea is extraordinarily high, e.g. 400 mg. per cent.

In advanced renal failure fibrillary muscle twitches are often seen; they are caused by anterior horn cell discharges of unknown cause, and are unrelated to any apparent change in calcium metabolism, though they can often be relieved by the intravenous administration of calcium

Cardiovascular

Hypertensive Vascular Disease. Hypertension and chronic renal failure are closely related (p 77) and, though hypertension may cause renal failure, the reverse is more common It is rare for the blood pressure not to rise in chronic renal failure, but its rise may produce few symptoms; when they occur they are due to widespread vascular changes or cardiac failure

The vascular lesions may be acute or chronic. They can nearly always be observed on inspection of the ocular fundus, where they produce certain characteristic disturbances of the retinal arteries and [illegible]

Hypertensive retinopathy is distinguished primarily by the presence of papilloedema which at first may be unilateral There are also flame-shaped or blotchy hæmorrhages fanning out from the optic disc, and multiple areas of white discoloration known as exudates. These have indefinite margins and are of uneven size and colour, a lack of precision and uniformity which has caused them to be called " soft " exudates They consist of collections of oedema fluid Sometimes the oedematous retina lies in folds radiating from the macula towards the optic disc, an appearance referred to as a macular star. Soft exudates and hæmorrhages may precede the development of papilloedema.

In arteriosclerotic retinopathy the retinal arteries become tortuous and narrow, either irregularly or evenly along their whole length. They characteristically cross the veins at right angles, as opposed to the more usual oblique direction, and at these crossings the veins appear to be compressed by the artery; this appearance is known as arterio-venous

nipping. It is due to an accumulation of connective tissue between the artery and the vein, so that in fact the vein, as it approaches the artery, is not compressed but obscured. Exudates are also seen, but they are "hard" as opposed to those seen with the acute vascular changes They are small and compact, they have definite, sharp margins, and are of a dense yellowish-white colour. Eventually they are found in clusters particularly spreading out radially from the macula; another form of macular star. As chronic vascular changes frequently precede by several years the onset of the acute changes it is not unusual to find arteriosclerotic and hypertensive retinopathy combined

Hypertensive retinopathy may cause varying degrees of visual impairment, depending on the degree of papillœdema and the site and extent of the hæmorrhages and exudates (particularly if the macula has been involved). The striking clinical finding, however, is that often both fundi may be severely affected without the patient being aware of any change in vision; with arteriosclerotic retinopathy visual symptoms are even less frequent.

The changes which hypertensive vascular disease may produce upon renal structure and function have been described on p. 81. When they are superimposed upon chronic renal failure, cardiac failure and a further deterioration in renal function may occur With malignant hypertension cardiac failure is often one of the presenting clinical features. There are acute attacks of paroxysmal nocturnal and postural dyspnœa, and eventually oedema with a permanently raised venous pressure. Deterioration in renal function is due to (1) the reversible renal vasoconstriction associated with cardiac failure, and (2) the local vascular lesions

The onset of *acute* vascular changes in the kidney is revealed not only by the sudden change in renal function but also by the onset of hæmaturia and increased proteinuria The deterioration in renal function due to the vascular changes associated with malignant hypertension is partially reversible if it has not progressed too far before treatment is started. How far the functional changes produced by chronic vascular changes are reversible is uncertain

Pericarditis. A painless, aseptic, fibrinous pericarditis often develops in the terminal phase of chronic renal failure Its cause is unknown.

Hæmatological

Anæmia, leucocytosis and a raised erythrocyte sedimentation rate are all common features of chronic renal failure

The cause of the anæmia is unknown, it appears that the main

feature is a depression of bone marrow function, directly proportional, though not necessarily caused by the rise in blood urea (Fig 42). Blood loss is not important except in advanced cases with a continuous slow leak from ulcers in the gastro-intestinal tract, or following a hæmatemesis or melæna. In the later stages of renal failure the red cell life is often shortened

It has been suggested that the anæmia of chronic renal failure is an adaptive process, on the assumption that the lowered hæmatocrit increases renal plasma flow and glomerular filtration rate. It is known, however, that moderate changes in hæmatocrit, in either direction, do not alter renal plasma flow and filtration rate in normal

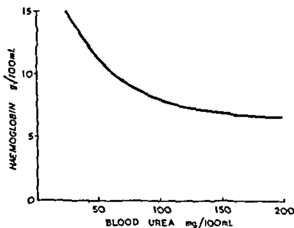


FIG 42 Schema of the mean relationship between the hæmoglobin concentration and the blood urea, individual plots show a considerable scatter

kidneys and that more severe changes produce a *fall* in glomerular filtration rate (p 71) It is true that if the hæmatocrit in a patient suffering from chronic renal failure and anæmia is suddenly raised by a transfusion there is a transient fall in glomerular filtration rate and rise in blood urea, but this would appear to be due more to a delay in the normal vasodilating response to a rise in hæmatocrit than evidence that the pre-existing low hæmatocrit was beneficial. This sharp fall in glomerular filtration rate, which often takes place upon transfusing cases of renal failure, may sometimes be fatal if the presence of kidney disease is unsuspected and transfusions are continued until the hæmoglobin is normal; the blood urea rises rapidly and the patient dies of acute renal failure Nevertheless, as acute hæmorrhage causes intense renal vasoconstriction, transfusions are occasionally

inevitable; and when chronic anæmia is sufficiently severe to cause, or contribute to the onset of cardiac failure, there will be an additional depression of renal function which may respond to small transfusions of packed cells

Respiratory

The deep sighing respirations of acidosis have already been mentioned. The other respiratory complications of renal failure are (1) "uræmic lung" and (2) infection.

"Uræmic lung" is a radiological diagnosis. It consists of dense bilateral opacities radiating from the hilum into the lung substance, while the upper and lower zones and the outer rim of the middle zones are clear. It occurs nearly always in patients with recurrent attacks of left ventricular failure, and it is debatable if the picture is distinguishable from that associated with recurrent left heart failure from other causes.

Pneumonia is frequently the immediate cause of death, but it is surprising that it usually develops only when the patient is already moribund It is not improbable that the deep respirations of acidosis and the rapid respiration of left heart failure prevent the bronchioles from becoming blocked and the lungs from collapsing, the usual preliminaries to pneumonia in semiconscious patients.

Cutaneous

The characteristic pigmentation of renal failure, together with the anæmia, give patients suffering from chronic renal failure a characteristic colour (p 129) The eyelids tend to be slightly swollen and an expression of tiredness and depression is common. It is not known why the eyelids should be swollen, but it is not due to an overall retention of salt and water.

In advanced renal failure there may be purpura, usually preceded and accompanied by bleeding gums; this is probably due to some capillary disturbance, the platelet count remains normal.

Pruritus is common and there may also be a variety of unspecific rashes, including erythema, vesicles and urticaria. The skin is often very dry because of dehydration; recurrent boils, carbuncles, and slowly healing scratches and abrasions are not infrequent.

Treatment of Chronic Renal Failure

Clearly it is of the utmost importance to try and identify the primary cause of the renal failure, for in some instances, e g. when it is due to infection of the renal parenchyma, obstruction of the urinary tract, or malignant hypertension, it may be possible to treat the

immediate cause of failure, and so prevent any further deterioration of function; often it may even be possible to obtain a large measure of improvement. Unfortunately, in most instances the cause of chronic renal failure is not treatable, for it is either unknown, or structurally irreversible, as with chronic glomerular nephritis, or congenital polycystic kidneys. Treatment is therefore mainly directed towards trying to delay and mitigate the consequences of advancing renal failure, particularly those following disturbances of water and electrolyte balance, retention of waste products, and hypertension. This may be very rewarding, for often much of the disturbance in renal function is reversible, having been caused by a vicious circle in which the disturbed renal function causes a change in the internal environment, which in turn leads to a further depression in renal function, e g renal failure → polyuria and nausea → dehydration → renal vasoconstriction → diminished glomerular filtration rate. If the secondary and reversible causes of renal functional impairment can be corrected or prevented the prognosis will depend entirely on the rate of progress of the primary renal disorder which is destroying the kidney. This rate varies in different diseases and from one individual to another with the same disease, often a patient may remain relatively well for a considerable time after the onset of chronic renal failure

Finally, when the patient is dying, symptomatic treatment can minimise much of the protracted misery of terminal renal failure.

Treatment of Biochemical Abnormalities

Water. It has been pointed out on p 22 that in normal man the amount of urea excreted in the urine is proportional to the urine flow up to urine flows of 2 ml./min (i e approximately 3 l./24 hr.), in chronic renal failure this relationship is still present and even appears to hold at greater urine flows. There is also evidence that a high turnover of water increases glomerular filtration rate A large fluid intake and high urine flow will therefore not only prevent dehydration but will also ensure a maximal rate of urea excretion. The advice to give a patient about his fluid consumption has to be decided for each individual. Some patients, particularly women, habitually drink very little, and they must be advised to drink rather more than they are accustomed to, i e. an extra three to four glasses of water a day. In the average case it is sufficient to point out that the fluid intake should be generous. The dangers of overhydration are minimal when water is being taken by mouth.

When severe dehydration has occurred through nausea, vomiting or diarrhoea it should be corrected immediately by the intravenous administration of 5 per cent. glucose, or half-strength saline. Occasion-

ally persistent but not particularly severe dehydration, developing simply from a distaste for fluids, may be relieved by 1 to 2 litres of water daily, given per rectum

Electrolyte and Acid Base Balance. Acidosis can be controlled to a certain extent by the daily oral administration of sodium bicarbonate 3–9 g. or sodium citrate 15–30 g., or by intermittent intravenous administration of sodium lactate. Sometimes, ammonium chloride is given to test renal function, or to increase the diuretic effect of [illegible] ronic

[illegible] r the nephrotic syndrome; the treatment of the former is discussed on p 138. Treatment of the nephrotic syndrome when combined with renal failure is awkward and difficult. A high protein diet must not be given, for it will raise the blood urea; resins are unmanageable because they aggravate the acidosis and precipitate rapid crises in potassium balance; and the administration of cortisone or prednisone often fails to cause a diuresis. The only procedures which are likely to be useful are mercurial injections and a low salt diet

Gross sodium chloride deficiency arising from excess urinary loss is rare in chronic renal failure, its treatment is dealt with on p. 149. Minor sodium chloride deficiency due to excess sweating, mild diarrhœa, or glycosuria can be avoided by ensuring that the salt intake is liberal It is always dangerous to restrict the salt intake of patients suffering from chronic renal failure, e.g. the use of a salt-free diet in the treatment of hypertension or migraine. The ability to conserve salt is limited and a contraction of the extracellular fluid space may develop insidiously with all its complications, particularly renal vasoconstriction, hypotension and deterioration in renal function.

Potassium retention is unusual in chronic renal failure, and only occurs as a terminal event. It may respond to 15–20 g. of cation exchange resin in the sodium phase, given orally three times a day. Potassium deficiency from excess urinary loss is also most unusual; its treatment is discussed on p 153

Calcium Metabolism. Osteomalacia, rickets and osteitis fibrosa can be cured by the administration of large quantities of vitamin D. The dose depends on the patient's response, but may have to be of the order of 3 mg of calciferol eight-hourly. Radiological improvement occurs within a few weeks and a return to normal in a few months. It is important to estimate the serum calcium concentration at frequent intervals, for it is easy to slip from the frying pan of calcium deficiency into the fire of hypercalcæmia

Urea and Other Waste Products of Protein Metabolism. The

concentration of urea in the blood is controlled by the rate of protein intake and the glomerular filtration rate (p. 24). In chronic renal failure glomerular filtration rate falls, the blood urea rises and there is a concomitant deterioration in the patient's general condition. As it is clear that urea is not directly responsible for this change, presumably it is due to the accumulation of other end-products of protein metabolism. For this reason alone the patient will feel better, and may survive longer, if protein intake is limited.

Another, more debatable, reason has been advanced for reducing protein intake. It has been pointed out that in chronic renal failure each remaining nephron has to excrete an increased quantity of solutes (p. 43), and that urea forms a large controllable fraction of this total. It has been suggested that the increased "work" that each nephron must therefore perform may accelerate its eventual destruction. It has been shown that in animals the renal lesions of senescence can be accelerated by a high protein diet, and that following unilateral nephrectomy and the removal of large portions of the other kidney, structural changes in the remaining renal tissue can be hastened by the administration of large quantities of protein. If these results are applicable to man then once renal failure has been diagnosed, protein intake should be reduced, whatever the initial concentration of blood urea. Generally, however, the therapeutic implications of these experiments are not accepted, and protein intake is regulated only to control symptoms. It is unusual to limit protein ingestion until the blood urea concentration rises above 70–100 mg. per cent, for symptoms of waste product retention rarely appear below these levels. A substantial fall in blood urea should be obtained without severe dietary difficulty or amino-acid deficiency, by reducing the daily protein intake to about 0.5 g. per kg. body weight (p. 321). During an acute deterioration of renal function it may be necessary, for a few days, to give a very low protein diet. This can most easily be done by giving the patient a rice diet (p. 322); if there is no oedema the rice can be cooked with salt in the normal way.

Treatment of Hypertensive Vascular Disease

Malignant Hypertension. If the patient has malignant hypertension the blood pressure must be reduced immediately, otherwise the prognosis is less than two years. The methods used to lower the blood pressure include the use of hypotensive agents, sympathectomy, and bilateral adrenalectomy. The hypotensive drugs include hexamethonium, pentolinium, hydrallazine, reserpine, mecamylamine and phenoxybenzamine (Dibenylene). The hypotensive agents are tried first, and the operations are reserved for those cases who do not

respond. The success of treatment depends not only on the ability of these procedures to lower the blood pressure but also on the ability of the kidneys to function at the lower pressure (p. 73); the latter probably depends on the extent of renal structural impairment before treatment is begun. If lowering the blood pressure raises the blood urea the position is hopeless To avoid this complication it is probably better to lower the blood pressure gently over a matter of days in order to allow the renal circulation time to adapt to the lower pressure (p 74). It is usually of no avail to try and reduce the blood pressure if the blood urea is initially greater than 100 mg. per cent., though occasionally the administration of reserpine followed by mecamylamine is successful. Reserpine is given alone for a few days, and later mecamylamine is added. If this combination is not effective, subcutaneous injection of hexamethonium or pentolinium is substituted for the mecamylamine. Reserpine administration is continued throughout, for it frequently potentiates the action of these other agents.

Adrenalectomy is usually performed on patients who are in a precarious condition, and has a high mortality. Sometimes it lowers the blood pressure and prolongs life when other methods have been unsuccessful Occasionally, it fails to lower the blood pressure but the acute vascular changes resolve and the patient becomes free from symptoms Sympathectomy is a safer procedure, but its effect on the blood pressure is even less predictable.

Non-Malignant Hypertension. Both in man and animals there is a close association between hypertension and sclerotic vascular lesions. In man the progress of renal damage from "non-malignant" hypertension is so slow that it rarely causes death from renal failure It is generally agreed, however, that renal function in chronic renal disease deteriorates more rapidly once there is a pronounced rise in blood pressure Accordingly it is considered reasonable and justifiable to try and lower a symptomless but *rising* blood pressure if there is any cause to believe that there is underlying renal disease

The same techniques to lower the blood pressure are used as in malignant hypertension except that surgical methods are not employed. In addition to the conventional hypotensive drugs, others such as chlorpromazine and phentolamine (Rogitine) may occasionally be useful. For some unknown reason these have little or no effect on hypertension from other causes (excluding pheochromocytoma), but may be useful in some cases of chronic renal failure. As in malignant hypertension the response of the kidney to the change in blood pressure

inued.

ds rapidly to bed

rest, morphia, digitalis and a low sodium diet ; mercurial diuretics are also used, but with more restraint than is usual in patients who have heart failure unassociated with renal failure (p 313) To prevent recurrences it is usually necessary to treat the hypertension (see above) which is the principal cause of the heart's failure

In advanced renal failure, cardiac failure may be most resistant to treatment. Rest in bed aggravates the dyspnœa so that it is better to sit the patient up in an armchair or a cardiac bed , digitalis overdosage is difficult to avoid, and a diuresis is unlikely even with mercurial diuretics ; lowering the blood pressure is now almost certain to depress renal function to lethal levels as will any attempt to correct the anæmia, which is also contributing to the cardiac failure.

Treatment of Anæmia and Blood Loss

The anæmia of chronic renal failure is unresponsive to almost all forms of therapy except the transfusion of red cells Packed red cells are given in small amounts (200 ml) on alternate days, for the risks of precipitating cardiac failure are relatively great and a transient deterioration in renal function almost inevitable (p 72). For these reasons packed red cells are inadvisable for those who have recently had cardiac failure, or in whom there is advanced impairment of glomerular filtration rate The administration of cobalt may occasionally stimulate hæmopoiesis, but its side-effects are so unpleasant that it is now rarely used It is customary to give iron preparations by mouth, though they are rarely effective

Hæmorrhage must be treated as rapidly as possible with transfusions of whole blood The dangers to renal function of under- and overtransfusion have already been mentioned

Treatment of Superimposed Infection

In patients with chronic renal failure an attack of acute pyelonephritis, however mild, may cause a severe reduction in renal function (p 216) Any suspicion of renal infection should therefore be treated promptly with antibiotics (p 223) The important point to remember about these infections is that clinically they may not be obvious , they should therefore be kept in mind when there is an otherwise unexplained deterioration of renal function

Infections elsewhere than in the kidney may also cause a deterioration of renal function but, with the exception of subacute bacterial endocarditis (p 208), these usually present fewer diagnostic difficulties

Treatment of Hiccough

There are many method of treating hiccough, including the

inhalation of carbon dioxide and the administration of chlorpromazine or mepyramine (Anthisan) The latter can be given in doses of 100 mg. four-hourly by mouth or by injection ; it is sometimes useful when all else has failed Occasionally a drop of oil of peppermint on a piece of sugar is sufficient to stop an attack.

Treatment of Nausea, Vomiting and Terminal Renal Failure

Nausea and vomiting may come on at any time, and they affect almost all patients during the final stages of renal failure. They are best controlled by chlorpromazine, given subcutaneously at first, and then by mouth In the terminal stages chlorpromazine not only abolishes nausea and vomiting, but it calms the patient's anxiety. It also reduces the quantity of drugs needed to control the other two distressing features of terminal renal failure, dyspnœa, and physical and mental restlessness. Morphia is useful for dyspnœa, and in combination with chlorpromazine will not cause nausea and vomiting If restlessness and distress are not sufficiently controlled by chlorpromazine and morphia, paraldehyde is given either as an enema or by intramuscular injection This induces a comforting drowsiness Barbiturates are also useful in this respect, but they are less reliable than paraldehyde, sometimes causing an unhappy, confused drowsiness which aggravates the restlessness

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14

THE ACUTE NEPHRITIC SYNDROME

THE acute nephritic syndrome consists of a sudden onset of oliguria, oedema, hypertension, raised jugular venous pressure and proteinuria, due to an abrupt disturbance of the kidney. In some patients one or more of these features may be absent, e.g. there may be no proteinuria, and yet it is clear that a modified acute nephritic syndrome has developed.

The acute nephritic syndrome may develop in a previously normal person, it may occur as a transient complication in chronic renal failure, or be superimposed upon a nephrotic syndrome. It may also *precede chronic renal failure, the nephrotic syndrome or acute renal* failure It is seen in a variety of diseases which affect the kidney, including all stages of glomerular nephritis, polyarteritis nodosa, anaphylactoid purpura, disseminated lupus erythematosus, and *following irradiation of the kidneys (Fig 43). It occurs most commonly* in acute glomerular nephritis.

Structural Changes in the Kidneys

The glomeruli usually show cellular hyperplasia, mainly endothelial with widening of the capillary walls, and varying degrees of inflammatory cell reaction In the more severe cases the tubules show focal areas of degeneration associated with clumps of inflammatory cells. On occasion an acute nephritic syndrome may occur without histological lesions

Functional Changes

Proteinuria is rarely greater than 2–5 g. per day, and there is an increased urinary excretion of red cells, granular casts and blood casts. As the urine is usually acid the hæmoglobin in the red cells changes to acid hæmatin and, if there is sufficient blood, the urine becomes dark brown. Lesser quantities of blood cause a smoky turbulence when the urine is gently shaken ; the presence of blood is confirmed microscopically. These urinary changes are directly related to the histological changes in the glomerular tufts, for when there is no proteinuria the glomeruli are normal.

Glomerular filtration rate is often reduced, but it is remarkable

how frequently the blood urea concentration remains within normal limits, if the patient previously had normal kidneys. In those with pre-existing renal disease and long-standing impairment of filtration rate, the further depression in filtration rate associated with the acute nephritic syndrome causes a substantial rise in blood urea

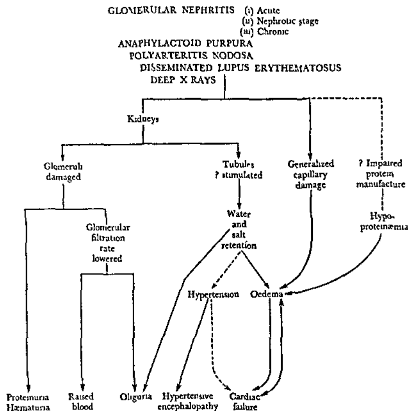


FIG 43 Diseases in which the acute nephritic syndrome may develop and some of the physiological disturbances which take place

The renal blood flow is usually unaffected except in the most severe cases and in those with pre-existing renal disease; when the blood flow is reduced the decrease is always proportionately less than that of the glomerular filtration rate, i e. there is a fall in filtration fraction

The ability to concentrate the urine varies with the degree of tubular damage; if the syndrome complicates established chronic renal failure there is nearly always a complete inability to concentrate,

Salt and water retention is due to an excessive tubular reabsorption of salt, of unknown cause, and is mainly responsible for the oedema. The characteristic distribution on the face and hands and the unusually high protein concentration of the oedema fluid make it very likely that generalised capillary damage also contributes to its formation. The acute salt and water retention causes an increase in weight, an expanded plasma volume, cardiac enlargement, and a fall in packed cell volume, hæmoglobin and plasma proteins. It is also very probable that salt and water retention is partly responsible for the concomitant cardiac failure and hypertension. Whatever precipitates the cardiac failure, once present it will also contribute to the accumulation of oedema by increasing tubular salt and water reabsorption. Hypoproteinæmia is usually minimal, but occasionally it is severe; it must then also contribute to the formation of oedema.

The cause of the hypoproteinæmia is obscure. The retention of water may cause a mild dilution of plasma proteins, and there may be a widespread leak of protein through damaged capillaries; in addition, it is possible that on very rare occasions a particularly heavy proteinuria may be partly responsible. Nevertheless, the acute fall in plasma albumen to below 1·0 g. per cent. which occasionally occurs in patients with acute *anuria* from glomerular nephritis makes it extremely likely that, at least in these cases, there has been a considerable diminution in protein production. It is possible that a diminished protein production is a contributory factor in the hypoproteinæmia found in the acute nephritic syndrome.

There is evidence of cardiac failure in almost all cases of the acute nephritic syndrome, whether or not there are suggestive symptoms, such as dyspnœa. The rise in jugular venous pressure and pulmonary crepitations are the most obvious clinical signs of cardiac failure, while the increased size of the heart radiologically, and the altered Valsalva response* is confirmatory evidence. Paroxysmal attacks of postural and nocturnal dyspnœa which are so characteristic of acute left ventricular failure are rare, but milder degrees of dyspnœa are relatively common The striking feature of the cardiac failure is that the heart rate is often either unchanged or slower than normal. In fact this combination of raised jugular venous pressure and bradycardia is often one of the most diagnostic features of the acute nephritic syndrome The cause of the cardiac failure is unknown;

The sudden onset of hypertension probably causes the bradycardia The extent of the rise in blood pressure varies a great deal and often it is so small that it is only noticed retrospectively, particularly in children The cause of the rise in blood pressure appears to be related to the salt and water retention, for it does not occur without oedema and a gain in weight, it also seems to be related to the histological changes in the glomeruli, though occasionally the blood pressure may be normal in the presence of extensive glomerular proliferation and exudative inflammation.

Clinical Features

At the onset the patient notices that the face, hands or feet are swelling or that the urine has changed colour to dark brown, or red. Very occasionally dyspnœa may be the presenting symptom, this is more likely in children or when there is pre-existing renal disease There are few other complaints, though upon direct questioning it may be possible to obtain a history of a recent gain in weight, oliguria, and lassitude Severe pain in the back often occurs with polyarteritis nodosa, and an ache in the loins seems to be a genuine feature of acute glomerular nephritis. Feverish symptoms and the extent of the rise in temperature vary with the cause of the syndrome Children often present with loss of appetite, and pallor

Progress depends a great deal on the disease with which the syndrome is associated, but in the majority of cases the signs and symptoms [illegible]

[illegible]

[illegible]

and some additional impairment of renal function may be permanent. In patients with previously normal kidneys, recovery is often complete, particularly with acute glomerular nephritis. Death during the acute phase of the syndrome is unusual, but may be caused by left heart failure, renal failure or hypertensive encephalopathy.

Treatment

Occasionally it may be possible to influence directly the disease which has precipitated the acute nephritic syndrome For instance, the use of adrenal steroids in polyarteritis nodosa Otherwise treatment is symptomatic and is aimed at preventing or minimising the effects of renal and cardiac failure and hypertensive encephalopathy until there is a spontaneous recovery.

It is convenient to keep a day-to-day chart of the fluid intake, urinary output, blood pressure, weight and 24-hour urinary protein excretion; 24-hour creatinine clearance should be estimated once a week.

Renal Failure. As renal failure is usually minimal and of short duration its treatment is not difficult. During the oliguric phase the patient is placed on a salt- and protein-free diet, and the daily fluid intake is limited to a volume equal to the urine passed in the previous 24-hours, plus 500 ml. to replace insensible loss. As soon as a diuresis starts, and the glomerular filtration rate returns to normal, these restrictions are relaxed.

In the rare cases when there is acute renal failure with either complete anuria or a daily urine output below 400 ml. with a specific gravity around 1·010, treatment is as described for acute renal failure from any other cause, except that measures taken to avoid acute cardiac failure have to be even more carefully observed than usual

Cardiac Failure. In most patients there is no necessity to treat the cardiac failure by other means than the salt and water restriction mentioned above. The dyspnœa of the onset usually settles after a few hours' bed rest, but if it increases it may be necessary to use [illegible]

[illegible] During a paroxysm of acute left heart failure with deepening cyanosis, hexamethonium 25 mg. intravenously may be life-saving. On general principles the use of mercurial diuretics is not advised and, in any case, they rarely succeed in producing a diuresis in an acute nephritic syndrome.

Hypertensive Encephalopathy. This exceedingly rare complication responds to the intravenous administration of barbiturates (sodium amylo barbitone or thiopentone). After the initial injection it is usually sufficient to continue sedation with large intermittent doses of barbiturates by mouth If these measures are not sufficient the fits can be controlled by lowering the blood pressure with methonium drugs, given either intravenously or intramuscularly

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15

RENAL FUNCTION AND LOSS OF "BASE" ELECTROLYTES*

THERE are two important links between loss of base and ren function: (1) Renal failure may be responsible for a negative balan of sodium, potassium or calcium, because they are lost in excessiv amounts in the urine; (2) a negative balance of sodium, potassium, o an excessive urinary excretion of calcium, may cause renal failure

SODIUM

Sodium Deficiency *due to* Renal Failure

The following renal diseases may sometimes be responsible for an excess urinary loss of sodium:

1. Chronic pyelonephritis.
2. Advanced chronic renal failure
3. During recovery from acute tubular necrosis.
4. Renal disease of moderate severity combined with dietary salt restriction.
5. Selective tubular inability to reabsorb bicarbonate (Renal Acidosis.

Sodium Deficiency *as a cause of* Renal Failure

The following conditions may occasionally cause such a loss of sodium that its deficiency contributes materially to the onset of renal failure

1. Severe diarrhœa, and vomiting (pyloric stenosis)
2. Post-operative gastric suction without replacement.
3. Intestinal and biliary fistulæ.
4. Diabetes
5. Acute pathological processes involving the brain.
6. Hypo-adrenalism (Addison's disease)
7. Mercurial diuretics.

* I e metallic cations

The signs and symptoms of sodium deficiency depend on the associated changes in water and chloride balance, i e

1. Sodium deficiency with chloride and water deficiency.
2. Sodium deficiency with chloride deficiency but excess water intake.
3 Sodium deficiency without chloride or water deficiency.

Clinical Features of Sodium, Chloride and Water Deficiency

Sodium loss is usually accompanied by chloride and water loss, the deficiency of the chloride is usually proportional to that of sodium, but the negative balance of water is usually smaller, for the patient often continues to drink. The extracellular fluid, therefore, tends to become hypotonic, and there is a transfer of water into the cells. The eventual signs and symptoms of sodium deficiency are thus a combination of those due to intracellular overhydration, and decreased extracellular fluid volume. The former gives rise to cerebral and the latter to cardiovascular abnormalities.

The patient is drowsy, restless, apathetic, and sometime unco-operative. There is thirst (despite the hypotonic plasma), headache, anorexia, nausea and postural giddiness; vomiting may occur and there is a liability to faint on standing; eventually muscle and abdominal cramps develop and the patient may pass into a muttering delirium. There is loss of weight, the face is haggard and the eyes sunken, the skin is clammy and cold and, on pinching, it tends to remain raised; the superficial veins are thin and constricted; the tongue dry, and the eyeballs soft, the pulse is rapid and both the mean arterial and the pulse pressures are decreased. The circulating hæmoglobin concentration is raised, but plasma sodium and chloride are lowered. If salt deficiency is not corrected the patient may die rapidly from peripheral circulatory failure.

It must be emphasised, however, that there may be a considerable loss of salt before there is much clinical evidence of deficiency. But even a subclinical deficiency is sufficient to cause renal vasoconstriction with a fall in renal blood flow and glomerular filtration rate, and an increase in blood urea When salt deficiency is secondary to renal failure the urinary specific gravity is around 1·010 whereas if the kidneys were previously healthy, tubular function remains normal and the specific gravity will at first be greater than 1·020. If, however, the vasoconstriction persists and acute renal failure develops, the specific gravity will fall towards 1·010. Proteinuria is nearly always present.

Ætiology and Diagnosis

Sodium, Chloride and Water Deficiency due to Renal Failure. Chronic pyelonephritis is the most common renal disease to cause florid salt

and water deficiency; it has also been reported with chronic glomerular nephritis and polycystic disease, the syndrome is sometimes known as "salt losing nephritis" Very rarely sodium deficiency may also occur during the recovery stage of acute tubular necrosis (p. 114) The chronic renal diseases which cause sodium deficiency may give rise to serious diagnostic difficulties (p 147) but the salt and water loss following acute tubular necrosis should be anticipated

Sodium, Chloride and Water Deficiency as a cause of Renal Failure
Salt and water deficiency following post-operative gastric suction, intestinal and biliary fistulæ should also be anticipated, the onset of renal failure in these conditions is often an indication of mismanagement

The risk of precipitating renal failure by giving low salt diets to patients suffering from renal disease has been mentioned earlier (p 136)

Renal failure from loss of water and salt caused by diarrhœa and vomiting or diabetic ketosis does not usually present any diagnostic difficulties But as a complication of acute cerebral conditions it may easily be overlooked (p 247)

The greatest diagnostic difficulty is in differentiating the sodium chloride deficiency and renal failure of Addison's disease from sodium chloride deficiency due to chronic renal disease In both the deficiency is due to a urinary leak of salt and in both there may be nausea, weakness, loss of weight, pigmentation and hypotension In an emergency the two conditions can be distinguished by the fact that the administration of hydrocortisone to patients with renal disease has no effect on the high rate of urinary salt excretion, while recovery occurs rapidly upon giving large amounts of salt and water When there is more leisure to make the diagnosis it will be found that in sodium chloride deficiency due to renal disease the urinary excretion of ketogenic and ketosteroids is normal, and that of aldosterone is raised, and that the excretion of the former is increased by the administration of ACTH

Treatment

This consists simply in the rapid intravenous administration of large amounts of isotonic saline, preferably with sodium lactate in a proportion of 2 to 1. Isotonic saline contains 150 mEq /l of sodium and 150 mEq /l of chloride, whereas the extracellular fluid contains 150 mEq /l of sodium but only 100 mEq /l of chloride; the administration of one litre of isotonic sodium lactate (150 mEq of sodium) for every two of saline ensures that sodium and chloride are given in physiological proportions If acute renal failure has already occurred the rate of infusion must be more moderate, for great care is needed to

prevent the onset of cardiac failure; it is also essential that sodium lactate be given, for the kidneys are unable to excrete the excess chloride in the sodium chloride solutions.

Some Factors of Sodium and Chloride Deficiency with Excess Water Intake

Occasionally patients who are suffering from salt deficiency and oliguria are inadvertently given water (5 per cent. glucose) intravenously. They may not excrete this water and they then develop acute overhydration with nausea, vomiting and mental confusion. Treatment consists in the intravenous administration of about 300 ml of hypertonic (3 per cent.) saline.

Some Factors of Sodium Deficiency Without Chloride or Water Deficiency

This occurs characteristically in chronic renal failure when the ability to excrete hydrogen and ammonium ions is impaired, an acidosis develops and there may be an increased excretion of sodium and other base electrolytes.

The condition is also seen when there is a decreased tubular ability to reabsorb bicarbonate (p 163), a rare congenital condition called Renal Acidosis.

Treatment consists of the administration of sodium lactate or bicarbonate

POTASSIUM

Potassium Deficiency *due to* Renal Failure

The following renal diseases may sometimes cause an excess urinary loss of potassium.

1. Chronic glomerular nephritis.
2. Chronic pyelonephritis
3. Polyarteritis nodosa.
4. During recovery from acute tubular necrosis.
5. Inability to reabsorb bicarbonate (Renal Acidosis).

Potassium Deficiency *as a cause* of Renal Failure

The following conditions may cause such a loss of potassium that its deficiency contributes materially to the onset of renal failure:

1. Prolonged vomiting, e g. pyloric obstruction.
2. Prolonged diarrhœa, e.g. small bowel insufficiency, excess use of purgatives, or enemas
3. Post-operative gastric suction.
4. Intestinal and biliary fistulæ.
5. Uncontrolled diabetes.
6. Injudicious use of ion exchange resins.
7. Aldosteronism

Clinical Features of Potassium Deficiency

Until potassium deficiency is advanced its signs and symptoms are vague and indefinite. The outstanding and characteristic feature of advanced potassium deficiency is the development of muscular weakness which progresses to paralysis and death from respiratory failure Otherwise there may be irritability, nausea, confusion and paralytic ileus The physical signs are apathy, loss of reflexes, loss of motor power, gasping respirations and occasionally irregularity of the heart rate If the potassium loss is due to renal disease the presence of which is unsuspected, many of these features may at first be thought to be due to hysteria

A certain diagnosis of low plasma potassium can only be made by direct estimation, though some information can be obtained from an electrocardiograph which shows flattened T waves, often with prominent U waves Though the plasma concentration of potassium is sometimes of value when the loss of body potassium is severe, it is often misleading, particularly when rapid shifts of potassium are taking place from one fluid compartment to another The cells may then be severely deficient in potassium though the plasma concentrations are normal or even high When potassium deficiency is primary and renal failure its consequence, the plasma bicarbonate is usually raised, but when potassium deficiency is due to renal disease the plasma bicarbonate is nearly always reduced because of the impaired ability to secrete hydrogen ions and ammonia which accompanies chronic renal failure. Alkalosis is due to a shift of hydrogen ions into the intracellular fluid, in exchange for intracellular potassium which is released into the extracellular fluid to prevent its concentration from falling to a lethal level Sodium ions also cross into the intracellular fluid in exchange for potassium so that in pure potassium deficiency there is an overall sodium retention

Presumably the renal failure which follows potassium deficiency is due to lack of potassium within the tubule cells, for both functional and histological changes are mainly found in the tubules. The ability to concentrate the urine is lost at an early stage though the ability to dilute remains for a considerable time, occasionally the urine may remain at a fixed concentration which is hypotonic to plasma. Polyuria and particularly nocturia are therefore distinctive features of renal failure associated with potassium deficiency There is also an inability to excrete a highly acid urine, and to excrete hydrogen ions at a normal rate following the administration of ammonium chloride, though the ability to excrete ammonia remains normal for a considerable time. Changes in glomerular filtration rate follow and are less severe than the tubular changes Nearly always there is a trace of protein in the urine.

The most characteristic histological change found in potassium deficiency is extensive vacuolation of the cells of the proximal tubule ; this change is rapidly reversible after potassium administration. The more advanced appearances are similar to those of chronic pyelonephritis and are not reversible.

Ætiology and Diagnosis

Potassium Deficiency due to Renal Failure. This is a rare phenomenon and is characterised by the continued excretion of substantial amounts of potassium in the urine despite depleted body potassium and low plasma potassium The renal disease responsible for such a deficiency is easy to diagnose when it occurs during recovery from acute tubular necrosis, but it is more difficult to distinguish when it is due to chronic glomerular nephritis, chronic pyelonephritis, polyarteritis nodosa or an inborn defect of tubular function. The most distinguishing feature of polyarteritis nodosa is pyrexia, which occurs in all cases, even when the only sites overtly involved are the kidneys.

The early stages of potassium deficiency due to an inborn error of tubular function (Renal Acidosis) may sometimes be differentiated from chronic destructive renal disease such as glomerular nephritis by the fact that with the former the impairment in glomerular filtration rate is moderate, and the ability to produce a highly acid urine and to excrete ammonia in response to ammonium chloride is grossly abnormal (p 164) With chronic destructive lesions, though there is also an impaired ability to excrete ammonia, glomerular filtration rate is severely reduced and the ability to excrete a highly acid urine remains normal until potassium deficiency itself impairs the ability to excrete an acid urine (see above).

Potassium Deficiency as a cause of Renal Failure. This syndrome is more frequent than its converse and its cause is usually more easily diagnosed. When potassium deficiency causes renal failure the loss of potassium is nearly always from the alimentary tract. Vomiting, gastric suction, diarrhœa, intestinal fistulæ and the misuse of ion exchange resins are easily identifiable causes of excessive loss of potassium. Long-continued use of purgatives and small bowel insufficiency may be more obscure, but there is usually some looseness of the bowels In all these conditions the urine contains only minimal amounts of potassium (p. 55) and except with ion exchange resins, the plasma bicarbonate is raised (p 168). This combination of renal failure, low plasma potassium and low urinary excretion of potassium, proves that the renal failure is indeed due to *extrarenal* loss of potassium

There are, however, two other situations in which renal failure is

caused by excessive *renal* loss of potassium, diabetic ketosis and primary aldosteronism. In diabetic ketosis (p 251) the potassium deficiency is only an incidental cause of renal failure and no diagnostic confusion is likely. Renal failure due to primary aldosteronism may be extremely difficult to differentiate from renal failure due to a moderately severe renal disease in which there is such an excessive urinary loss of potassium that instead of acidosis there is alkalosis In both there may be polyuria and thirst, low plasma potassium, hypertension and little disturbance to the concentration of blood urea The distinction has to be based, therefore, on finding a raised urinary excretion of aldosterone, and evidence of a general tendency to increased retention of sodium and increased excretion of potassium When aldosterone excretion is 20 to 30 times greater than normal the diagnosis of aldosteronism is unequivocal, but there are cases in which an adrenal tumour containing large amounts of aldosterone has caused potassium deficiency and renal failure, and yet the urinary excretion of aldosterone has been within the upper normal range. The correct diagnosis may still be suspected on the grounds that, except in aldosteronism, potassium deficiency is associated with a low normal urinary excretion of aldosterone

Indirect evidence of primary aldosteronism includes the salivary sodium potassium ratio, and renal biopsy findings Aldosteronism is extremely likely if the salivary sodium potassium ratio is below 0·4, while it is excluded by a ratio greater than 1 0 Renal biopsy can sometimes be useful if the structural changes are characteristic only of potassium deficiency, i e there is vacuolation of the tubule cells, particularly the distal tubules, it is of no help if the lesions are more extensive and include those of pyelonephritis In cases where a doubt remains laparotomy is justified.

Treatment

When renal disease is the cause of the potassium deficiency the only effective treatment is potassium replacement followed by the daily oral administration of sufficient potassium to balance the excess urinary loss Potassium citrate or acetate, together with sodium bicarbonate or lactate, are given when there is acidosis, potassium chloride when there is alkalosis

To prevent the onset of potassium deficiency during the early diuretic phase of acute tubular necrosis it is usually only necessary to give plenty of orange and tomato juice, figs, apricots, dates and meat extracts, all of which contain high quantities of potassium (p 324).

When potassium deficiency is due to excess alimentary loss all that is required is to replace the potassium and stop any further loss, if the

latter is not possible (e g. intestinal fistulæ, *gastric suction*) *potassium* should be given intravenously at the same rate as it is being lost.

Potassium is best given intravenously when there is a good urine flow, in order that an excess plasma potassium may more easily spill over in the urine. It is also wise to avoid intravenous administration for 24 hours after any particular stress such as an operation, for at these times the plasma potassium is apt to be raised whatever the concentration in the cells. It should also be borne in mind that in normal circumstances, though the total body potassium is about 2,500 mEq , the amount in the extracellular fluid is only 75 mEq. and that death occurs if it rises to 150 mEq. Cardiac arrest from hyperpotassæmia occurs at plasma levels of 9–10 mEq /l., so that it is generally wise not to give potassium intravenously at a greater rate than 25 mEq per hour It is also best to limit the concentration of the fluid to 40 mEq /l., for higher concentrations are liable to cause painful spasm of the vein.

If a patient suffering from a pure potassium deficiency is given saline instead of potassium there is likely to be increased sodium retention with oedema and an increased urinary excretion of potassium

CALCIUM

A raised urinary excretion of calcium may cause renal failure irrespective of the overall calcium balance The reason for this is

[illegible]

deficiency of potassium ions, or the renal failure of sodium deficiency which is due to contraction of the extracellular fluid volume and renal vasoconstriction.

The following conditions are associated with a high urinary calcium excretion and renal failure

Increased Urinary Excretion of Calcium *due to* Renal Failure

The renal diseases known to cause a great increase in urinary calcium excretion are those in which there are specific defects of tubular function :

1. Inability to reabsorb phosphate (p. 162).
2. Inability to reabsorb calcium (p. 163).
3. Inability to reabsorb bicarbonate (Renal Acidosis, p 163).

Increased Urinary Excretion of Calcium *as a cause of* Renal Failure

(*a*) Following increased calcium absorption:

1. Compulsive milk drinking.

2. Vitamin D intoxication.
3. Sarcoidosis.
4. Idiopathic hypercalcæmia of infants.
5 ? idiopathic hypercalcuria.

(b) Following an increased rate of bone decalcification.

1 Hyperparathyroidism.
2. Diffuse carcinomatosis of bone.
3 ? myelomatosis

Clinical Features Associated with Hypercalcuria

As the renal failure is only related to the high urinary excretion of calcium and not to negative calcium balance (unlike potassium and sodium), the general signs and symptoms vary widely from one cause to another For instance, if the hypercalcuria is secondary to bone disease there will be a negative calcium balance and signs and symptoms of bone softening or fractures, whereas if hypercalcuria is due to excessive intestinal absorption of calcium there will be calcium equilibrium and no signs or symptoms of bone disease.

The type of renal failure which develops has a certain constancy whatever its origin, and closely resembles the renal failure found with potassium deficiency There is polydipsia and polyuria, often of such severity that the patient may at first be thought to be suffering from diabetes insipidus But dehydration or the administration of pitressin shows severe impairment of concentrating capacity whereas the ability to dilute remains for a considerable time, frequently the urine remains fixed at a concentration below that of plasma At first the blood urea is only moderately raised to about 50–60 mg. per cent But conditions which give rise to increased calcium excretion may persist for many years and gradually so many nephrons are destroyed that eventually the clinical picture is the same as in chronic renal failure from other causes

Hypercalcuria is usually present when the serum calcium is raised, but it may also be present without such a rise An excessive urinary excretion of calcium may be diagnosed by doing a modified calcium balance (p 56) As a rough approximation a random sample of urine may be tested with Sulkowitch's reagent (p 56), if a thick white precipitate forms rapidly, the diagnosis of a raised calcium excretion is definite Occasionally, when the urinary excretion of calcium is extremely high, i e. around 1,000 mg a day (on a normal diet the usual range is 80–300 mg.), the urine upon standing will develop a thin white chalky precipitate which is characteristic. In the early stages renal biopsy may show no abnormality, but later precipitated calcium can be seen as clumps between and across the

nephrons, and as a fine dusting in the tubule cells and basement membrane. Some tubules eventually atrophy and varying numbers of glomeruli become structureless round eosin staining masses. In long-standing cases the deposition of calcium in the kidney can be seen radiologically.

Ætiology and Diagnosis

Increased Urinary Excretion of Calcium due to Renal Failure

Though chronic renal failure due to destruction of nephrons may be associated with a small increase in calcium excretion there is no evidence that this ever increases the severity of the renal failure or that it contributes seriously to any of the bone changes which occur in chronic renal failure (p. 127).

There are some inborn errors of tubular function, however, in which a high urinary excretion of calcium may cause severe osteomalacia and a partially reversible impairment of renal function. This is best seen in those suffering from an inability to make an acid urine and who therefore excrete calcium in order to cover the excretion of fixed anions (p. 163), if sodium and potassium salts are given in sufficient amounts they are excreted in place of calcium, and renal function may improve considerably.

When the increased urinary excretion of calcium is due to renal disease, the serum calcium is usually depressed ; whereas when the increased calcium excretion is the cause of renal failure the serum calcium is often raised.

Increased Urinary Excretion of Calcium as a cause of Renal Failure

(*a*) *Following Increased Calcium Absorption.* In compulsive milk drinking, vitamin D intoxication, sarcoidosis, idiopathic hypercalcæmia of infants and idiopathic hypercalcuria there is an increased alimentary absorption of calcium and the following sequence: hypercalcæmia → hypercalcuria → renal failure.

Compulsive milk drinking is a rare condition which, initially, can easily be overlooked, for the patient may fail to disclose his idiosyncrasy, or he minimises its extent. Frequently the milk drinking begins because of recurrent dyspepsia, but as the amount taken increases and hypercalcæmia develops, the dyspepsia becomes worse. The fact that these patients are also apt to take large quantities of alkalis may increase the liability of calcium to be deposited in the kidney.

Unequivocal vitamin D intoxication is rare. In adults it occurs as a form of food fad, and in infants and children from over-solicitous motherly attention. There is increasing evidence that infants and children may normally ingest larger quantities of vitamin D than are

y, for not only is it given as concentrated cod and halibut liver much of the food they eat, such as milk preparations and have vitamin D added in substantial quantities This excess the cause of the increased calcium absorption of idiopathic cæmia of infants.

increased calcium absorption of sarcoidosis also appears to be vitamin D, not excess ingestion, but rather to a hyper-ty to normal amounts either in the food or following exposure ght. Idiopathic hypercalcuria may be due to the same enon There are certainly some cases who have an increased ry calcium absorption, hypercalcuria and sometimes hyper-a in whom there is no evidence of sarcoidosis, but who respond al steroids in the same way as the hypercalcuria of sarcoidosis; ally one of these patients develops sarcoidosis at a later date ses with idiopathic hypercalcuria, however, fail to respond to e treatment

ollowing Increased Rate of Bone Decalcification There are three ns to be considered hyperparathyroidism, diffuse carcinoma-bone and myelomatosis

diagnosis of hyperparathyroidism depends on the finding of a sma phosphate, hypercalcæmia and hypercalcuria; the eristic periosteal erosions in the bones of the hands and alveolar, bone cysts, a raised alkaline phosphatase and recurrent renal nay also occur It is the condition which gives rise to the serum calcium concentrations, sometimes over 20 mg per Acute hyperparathyroidism with severe prostration, muscular ss, pains and tenderness, vomiting, cardiac failure, dyspepsia, a and polydipsia may not be recognised, unless the diagnosis is ed on every occasion that there is unexplained thirst and a Radiological bone lesions may be absent both in acute and hyperparathyroidism, which makes the differentiation from osis or idiopathic hypercalcuria difficult. The confusion is if renal failure is moderately advanced, for this occasionally the plasma phosphate to rise and thus obscure one of the most eristic signs of hyperparathyroidism If renal failure is not advanced an infusion of calcium gluconate is sometimes of help fying the diagnosis, the normal response is a decrease in phosphate excretion, which does not occur in hyperpara-ism but can be obtained in sarcoidosis and idiopathic hyper-a. A distinction can also be made with a therapeutic trial of *steroids, which will control the excess calcium absorption from* t and the consequent hypercalcæmia and hypercalcuria of osis (and vitamin D intoxication), but has no effect on the

blood calcium and hypercalcuria of hyperparathyroidism; while in idiopathic hypercalcuria adrenal steroids are liable to *increase* the rate of calcium excretion. Finally it has recently been found that whereas the serum concentration of ionised calcium in hyperparathyroidism is always raised whatever the total concentration of serum calcium; in idiopathic hypercalcuria the concentration of ionised calcium is normal.

Diffuse carcinomatosis of bone is easily identified by X-rays of the skeleton and there may be an erythroblastic anæmia.

Whether the renal failure associated with myelomatosis is due to increased urinary calcium excretion is doubtful. Hypercalcæmia does occur, but it is due to hyperproteinæmia and, though renal calcification is often found, it is not extensive.

Treatment

The treatment of those innate tubular defects which give rise to hypercalcuria is discussed in Section 16

The increased calcium absorption in sarcoidosis is treated with cortisone, as this functional peculiarity is often phasic, treatment should be interrupted now and again to see if it is still necessary.

Idiopathic hypercalcæmia of infants will usually respond in a few weeks when treated with either a low calcium diet or cortisone; the latter allows a much greater flexibility in the diet, and calcium ingestion

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16

INNATE FUNCTIONAL DEFECTS OF THE RENAL TUBULES

THIS term has been suggested by Jackson and Linder, whose classification of these abnormalities is given below.

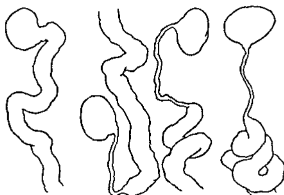
Fanconi was the first to suggest that inborn disturbances of selective tubular function might be the cause of certain rare forms of rickets. He described a syndrome in which there was hypophosphatæmia, glycosuria and amino-aciduria due to inadequate tubular reabsorption of each of these substances. Since this original description it has been recognised that a gradual reduction of glomerular filtration rate also occurs, so that it has been suggested that there may also be a primary defect in the glomeruli. Nevertheless, it is the tubular lesions which usually cause the patient's initial symptoms and signs and from which he may succumb before there has been a material rise in blood urea

Since these cases were first described there have been several reports of cases similar in type to this original syndrome but differing from it in certain respects It appears that cystinosis, i e the widespread deposition of cystine, occurs in many cases, and there have been reports in which at least one of the following abnormalities was present in addition to the classical features of the Fanconi syndrome described above: poor ammonia production, acidosis, hyperchloræmia and nephrocalcinosis, polyuria. In contrast, some cases have had no glycosuria, and others have not suffered from rickets Jackson and Linder point out that "These various cases indicate that there is probably no single invariable finding in the Fanconi syndrome if the wider concept is used, whereas many obviously homologous cases cannot be termed 'Fanconi syndrome' if a strict definition is applied The term 'multiple defects of tubular function' covers them all." If such a unifying concept is accepted then it is logical to include those conditions in which there is only a single tubular defect, but Jackson and Linder point out that though "these syndromes are all comparable in being largely explicable by specific defects of renal tubular function, they are not necessarily related as regards their primary cause" They suggest that these conditions may be listed as follows:

Unifactorial conditions .	
Inability to reabsorb ·	
Water	Renal diabetes insipidus
Phosphate	Vitamin D resistant rickets, early or late (R R D* of McCance, 1947)
Glucose	Renal glycosuria
Cystine and other amino-acids	Simple congenital cystinuria (Dent and Rose, 1951)
Calcium	Idiopathic hypercalcuria (McCune and Pray, 1940, Albright and Reifenstein, 1948)
Bicarbonate	Hyperchloræmic nephrocalcinosis Renal acidosis (Latner and Burnard, 1950).
Excessive reabsorption of	
Phosphate .	Pseudohypoparathyroidism (Albright, 1942)
Multifactorial conditions (probably all one disease, the " Fanconi group ")	
Inability to reabsorb	
Phosphate and sugar .	Glycosuric rickets, or osteomalacia
Phosphate, sugar and amino-acids†	Fanconi syndrome

* Raised resistance to Vitamin D

† Often associated with inability to reabsorb water, albumin(?), and fixed base, and to form ammonia, glomerular defect, organ cystinosis,



Fig

J Path Bact)

It has recently been shown, by means of microdissection of individual nephrons from cases who have died from the Fanconi syndrome, that the condition is associated with a characteristic structural lesion (Fig 44). The proximal tubule is shorter than normal and is connected to its glomerulus by an abnormally long and narrow neck quite unlike

anything seen in normal subjects. The epithelium in the neck regular, and it is considered that this is a primary lesion and secondary to prolonged tubular dysfunction. It is possible t congenital structural inadequacy of the proximal tubule may contrib to the overall defect in tubular function, whether or not there are a specific metabolic errors of the tubule cells.

Inability to Reabsorb Water

This condition is known as renal or nephrogenic diabetes insipid It is described on p 234.

Inability to Reabsorb Phosphate

This condition was first described under the title of Vitamin Resistant Rickets It is characterised by rickets in children a osteomalacia in adults, a low plasma concentration of phosphate, a an abnormally high urinary phosphate clearance. The renal distur ance of function is identified by measuring the phosphate to creatini clearance ratio (C_{PO_4}/C_{Cr}) · the upper limit of normal of this ratio 0·2, and when there is an inability to reabsorb phosphate it is raise Unfortunately the test is inaccurate when the creatinine clearance depressed below about 50 ml./min , and is not specific, for the ratio also raised in hyperparathyroidism. A tubular defect in phosphat reabsorption can sometimes be differentiated from hyperparathy roidism by giving phosphates intravenously and calculating the ren phosphate threshold ; this is lowered when there is an intrins tubular defect of phosphate absorption, and normal in hyperparathy roidism In addition, the serum concentration of ionised calcium i hyperparathyroidism is increased

Treatment is with calciferol 2–5 mg./day together with a high phosphorus diet, and the administration of $Na_2HPO_4 2H_2O$ 10 g /day. Frequently the condition does not respond or there is only a transient improvement.

Inability to Reabsorb Glucose

This condition is known as renal glycosuria and is discussed on p. 249

Inability to Reabsorb Cystine and Certain other Amino-acids

There are two forms of this disability. In one, the only clinical complication is the recurrent formation of renal calculi made of cystine, which are translucent to X-rays ; the urine always contains an excess of other amino-acids, but their loss and excess urinary excretion does not produce any clinical abnormalities

The other form, cystinosis, is characterised by a widespread deposition of cystine. Clinically, this is most evident in the corneæ, which develop a ground-glass appearance; occasionally cystine stones are also formed. In this form of the disease it is usual to find other serious tubular defects and some impairment in glomerular filtration rate.

Inability to Reabsorb Calcium

This condition is also known as idiopathic hypercalcuria. Its diagnosis, with its implication that the tubules are primarily at fault, is inferred after investigations have failed to demonstrate any other known cause of hypercalcuria. The patients present with calcium deficiency (p. 155), or renal stones; the serum calcium concentration is within normal limits; and occasionally the plasma phosphorus concentration is low

Those conditions in which the hypercalcuria is due to hypercalcæmia can be readily distinguished, but there are two other conditions in which the urinary calcium excretion is raised though the serum calcium is normal: Renal Acidosis (see below), and some cases of hyperparathyroidism. Renal Acidosis is easily differentiated by the low plasma bicarbonate, hyperparathyroidism is more difficult to distinguish. In some cases of idiopathic hypercalcuria the response to the intravenous administration of calcium will be normal, i.e. a decreased urinary phosphate excretion, in contrast to the lack of response which occurs in hyperparathyroidism; but this test often gives equivocal responses and the differentiation between idiopathic hypercalcuria and hyperparathyroidism may not be possible.

Inability to Reabsorb Bicarbonate (Renal Acidosis)

This condition is also known as hyperchloræmic acidosis or hyperchloræmic nephrocalcinosis

The outstanding abnormalities of tubular function are an impaired ability to excrete an acid urine and to excrete hydrogen and ammonium ions. In consequence there is an acidosis and an impaired reabsorption of bicarbonate, and the excretion of metallic cations (sodium, potassium and calcium) may also be increased The increased excretion of potassium may give rise to potassium deficiency (p 151), and the increased excretion of calcium to osteomalacia (p 155) The most frequent clinical presentation is that of osteomalacia

The fall in plasma bicarbonate which accompanies the diminished excretion of hydrogen ions and the impaired reabsorption of bicarbonate, is accompanied by an increase in extracellular chloride. Often, therefore, the diagnosis is first suspected by a finding of hyperchloræmic acidosis Usually the creatinine clearance and blood

urea are either normal or only moderately impaired so that the fall in plasma bicarbonate is out of proportion to the mild rise in blood urea, i.e a plasma bicarbonate of 15 mEq./l. with a blood urea of 45 mg. per 100 ml The diagnosis is confirmed by finding that though there is an acidosis the urine *p*H is around 6·5 and that the excretion of ammonium and hydrogen ions is low ; it is rare for the urine *p*H to fall below 6 0 or the ammonium excretion to rise above 50 mEq /day ; as might be expected there is little or no response to the administration of ammonium chloride. There is also severe impairment in the ability to concentrate the urine even when the glomerular filtration is almost normal.

Nephrocalcinosis occurs in most cases whether or not there is hypercalcuria, and renal calculi are common.

The diagnosis of Renal Acidosis has occasionally been made after an abdominal X-ray, taken for some other purpose, has shown the appearance of *nephrocalcinosis. Some of these patients have had* a normal plasma bicarbonate, for they have had no impairment in their ability to excrete ammonium ions. They have been considered to be suffering from the renal lesion which usually causes Renal Acidosis because of their inability to excrete a highly acid urine and a severe impairment in the ability to concentrate.

Treatment consists in the administration of alkalies, i.e. sodium citrate (there is no danger of giving an excess, for it is promptly excreted). In addition, calcium deficiency is treated with calcium lactate and calciferol, and potassium deficiency by the administration of potassium citrate. Renal Acidosis in children can usually be controlled and often there may be a spontaneous recovery. In adults treatment may be more difficult and recovery is unusual.

Excessive Reabsorption of Phosphate

This extremely rare condition is also known as pseudohypoparathyroidism The patient presents with attacks of tetany or fits, and the diagnosis is made by finding a high plasma phosphate concentration and a low serum concentration of calcium which are not influenced by injections of parathormone. There are no other abnormalities of renal function. These patients have characteristic round flat faces with small bulbous noses, thin, straight mouths, and strabismus; they also have short stumpy hands with stunted metacarpals. They are usually mentally retarded.

Inability to Reabsorb Phosphate, Sugar, Amino-acids, etc.

If the tubular defects are only those of phosphate and glucose reabsorption the condition is known as glycosuric rickets Except for

he glycosuria the clinical features are identical to those described above when there is a simple inability to reabsorb phosphate.

When the tubular defects include not only impaired reabsorption of phosphate and glucose but also of amino-acids, the condition is known as Fanconi's syndrome. The tubular defects are rarely limited only to those three abnormalities, and usually there are also defects of water reabsorption and an inability to form an acid urine

Fanconi's syndrome is a rare familial condition which usually becomes manifest before the age of 15 The patients usually present with underdevelopment, rickets, thirst and polyuria On examination they are short, squat and often show opaque deposits of cystine in the corneæ. Apart from the characteristic urinary findings there is always proteinuria, and usually some impairment of glomerular filtration rate The plasma phosphorus is low and the blood urea raised. When there is an inability to excrete an acid urine there is hyperchloræmic acidosis, together with the passage of an alkaline urine.

The prognosis is variable. A few patients survive for years with suitable treatment and some have married and had children

Treatment of the defects of phosphate reabsorption and acid excretion have been mentioned above

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17

RENAL FUNCTION AND ALKALOSIS

RESPIRATORY ALKALOSIS

THE changes in renal function which take place with a respiratory alkalosis have been mentioned on p 48.

METABOLIC ALKALOSIS

The renal responses to a pure metabolic alkalosis consist in an increased excretion of sodium, potassium and bicarbonate (p 48). The normal kidney's ability to deal successfully with a severe, persistent metabolic alkalosis is now well recognised For instance, it has recently been shown that if patients suffering from peptic ulceration are treated with a continuous intragastric drip of 1,000 mEq of sodium bicarbonate (84 g) per day for three weeks there is a persistent rise in plasma bicarbonate, but no apparent change in renal functional efficiency, and in fact the glomerular filtration rate tends to rise and the blood urea to fall

Nevertheless in clinical practice the combination of alkalosis and renal failure occurs relatively frequently, and until recently it has been considered that the alkalosis was the cause of renal failure The evidence mentioned above, however, contradicts this conclusion and the true position is more complex Excluding increased ingestion of sodium bicarbonate, alkalosis is caused by either a deficiency of hydrogen, or potassium (see below). The connection between potassium deficiency and renal failure has been discussed previously (p 151), while the connection between hydrogen ion deficiency and renal failure is best discussed in relation to the most common syndrome in which renal failure and alkalosis occur, i e pyloric obstruction, in which it will be seen that potassium deficiency may also contribute to the alkalosis, and the renal failure

Pyloric Obstruction

Gastric juice contains water in which there are approximately 145 mEq/l of chloride, 83 mEq/l hydrogen ions, 50 mEq./l of sodium, and 12 mEq/l of potassium Following the persistent vomiting of pyloric obstruction there develop deficiencies of water, hydrogen ions, chloride, sodium and potassium and, occasionally, there is the

further complication of a gastro-intestinal hæmorrhage. Each of these gives rise to its own *sequence of disturbance in body fluids*, and renal function. It is important to realise that the direction of some of the renal functional disturbances depend on the pattern of the deficiencies, i.e. there may be oliguria or polyuria, an alkaline urine or an acid urine. The relative proportions of these deficiencies determine which functional changes will predominate.

Fig 45 illustrates the changes which may occur.

Factors Involved in the Renal Failure of Pyloric Obstruction

Water and Blood Loss. The continuous loss of water (with sodium and chloride) reduces the volume of all fluid spaces including the blood volume, and this is followed by consequences which have been described previously, i.e. renal vasoconstriction → reduced glomerular filtration rate and rise in blood urea. These changes will be more pronounced if there is also gastro-intestinal bleeding; in rare instances acute renal failure develops. Usually the renal ischæmia stops short of tubular necrosis and there is only *oliguria* with a urine concentration which tends to be raised.

Hydrogen Ion and Chloride Loss. The loss of hydrogen ions is the main cause of the alkalosis in pyloric obstruction, but both the loss of hydrogen and chloride ions cause a rise in plasma bicarbonate. The kidney's response to the metabolic alkalosis is to excrete an *alkaline urine*, containing large quantities of bicarbonate, sodium and potassium (p 48); a compensating mechanism which unfortunately accentuates the sodium and potassium deficiency caused by the vomiting.

Potassium Loss. The consequences of potassium loss on renal function have been described on p. 151. There is some reduction in glomerular filtration rate, but the most marked feature is *polyuria* with a urine concentration which remains iso- or hypotonic. Plasma potassium is low, and to compensate for this there is a shift of potassium from the intracellular space to the plasma and extracellular space, and a reverse shift of hydrogen and sodium ions from the extracellular space into the cells The loss of hydrogen ions from the plasma results in a rise in plasma bicarbonate, the other cause of alkalosis in pyloric obstruction

Sodium Loss. The vomiting and the excretion of an alkaline urine cause a deficiency of body sodium. Nevertheless, because the vomit contains relatively more water than sodium the concentration of plasma sodium is sometimes raised. Usually, however, the patient's thirst forces him to drink water, and this selective partial replacement of water to the exclusion of sodium lowers the plasma concentration of sodium below normal.

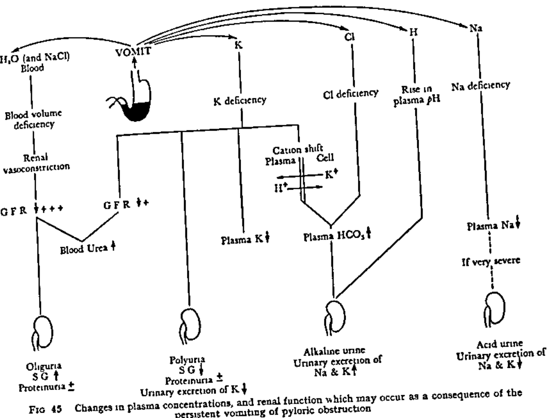


Fig 45 Changes in plasma concentrations, and renal function which may occur as a consequence of the persistent vomiting of pyloric obstruction

If sodium and potassium deficiency become sufficiently severe the *urine is acid*, though the plasma is becoming increasingly alkaline This is due to the effect of complete tubular reabsorption of sodium and lack of available potassium on the cation exchange mechanism in the distal tubule) If sodium reabsorption is nearly complete and there is no available potassium, some of the sodium ions reabsorbed in the distal tubule will be replaced by hydrogen ions and the urine will become acid.

Chronic Renal Disease. It is obvious that if there is some antecedent impairment of renal function the onset of pyloric obstruction and vomiting will cause a rapid deterioration of renal function At one time it was considered that renal failure with alkalosis could only occur if renal disease was already present before vomiting began

Alkalies and Milk. The most frequent accompaniment of pyloric obstruction is peptic ulceration, for which patients take both alkalies and milk Once the glomerular filtration rate begins to fall because of dehydration or potassium deficiency, the continued administration of sodium bicarbonate is not only useless but rapidly aggravates the alkalosis.

The importance of the high ingestion of calcium (in milk) in the incidence of renal failure in pyloric obstruction is not known, but hypercalcuria is known to impair renal function (p. 154).

Treatment of Metabolic and Renal Consequences of Pyloric Obstruction

Upon admission to hospital, most patients with benign pyloric obstruction cease to vomit and quickly begin to correct their electrolyte and water deficiencies almost unaided During the first few days it is customary to wash out the stomach before meals. Water and food then pass through the pylorus and are absorbed in normal amounts ; in such patients it is only necessary to make sure that they are given a mixed diet and that it is relatively low in protein until the glomerular filtration returns to normal levels

Occasionally, however, it may be necessary to accelerate recovery by giving electrolytes and water intravenously or in additional amounts by mouth. Isotonic saline is given intravenously in sufficient quantities to correct *hæmoconcentration*, *peripheral vein constriction* and tachycardia It is always wise to give potassium by mouth even if plasma potassium concentration is normal, for there may be potassium deficiency *without much change in plasma potassium* If plasma ... potassium should ... or 5 per cent. ... dium chloride ... usly, for if the should not be given ...

odium is retained the rate of potassium excretion is liable to increase.
The use of ammonium chloride to correct an alkalosis which is due potassium deficiency is also positively harmful The chloride is i mediately excreted in the urine together with cations, much of w ch may be potassium As it is nearly always impossible to decide to hat extent an alkalosis is due to potassium deficiency (except by iso e techniques, or by hindsight with balance measurements) it is ammonium chloride to correct alkalosis in any iated with gastro-intestinal fluid loss
be avoided until renal function has recovered and ny evidence of electrolyte deficiency.

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18

RENAL DISTURBANCES FOLLOWING URETERO-COLIC ANASTOMOSIS

When the bladder is severely diseased it may be *necessary to* implant the ureters into the walls of the colon. Theoretically, all the contents of the urine should then be evacuated *per rectum*, but as the

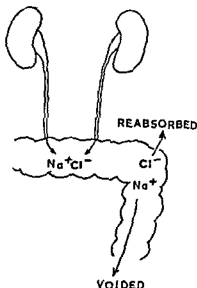


Fig. 46 Uretero-colic anastomosis. Schema to illustrate that in the colon the chloride ions excreted by the kidney are reabsorbed to a greater extent than those of sodium

urine passes down the colon, some of its contents are reabsorbed. One of the important features of this reabsorption is that chloride is reabsorbed to a greater extent than sodium (Fig. 46). There is also a *tendency for these patients to become acidotic,* and this is probably related to the *increased chloride reabsorption, though the exact* mechanism is not known. The possibilities are : (1) That the chloride [illegible] are reabsorbed in exchange for bicarbonate ions, or (3) that [illegible]

chloride ions are reabsorbed as ammonium chloride, for when the urine urea enters the gut much of it is changed into ammonia.

If the patient is not to become acidotic and oedematous (from the sodium reabsorption) the kidneys have to compensate for the intestinal reabsorption by excreting increased quantities of sodium, chloride, hydrogen and ammonium. After a few months the initial difference between the rates of chloride and sodium reabsorption becomes less marked and the tendency to acidosis ceases

The other complications of uretero-colic anastomosis are renal infection and partial or complete ureteric obstruction (occasionally both of these may have been present before operation, due to the disease in the bladder) Both infection and ureteric obstruction impair tubular function, including the ability to excrete hydrogen and ammonium, so that they may cause a rapid onset of severe acidosis. The nausea of acidosis diminishes the spontaneous intake of water and eventually it may cause vomiting, considerable dehydration, and contraction of the extracellular fluid volume Dehydration, renal infection, ureteric obstruction and acidosis can each depress glomerular filtration rate; together they may rapidly cause death from acute renal failure

These hazards are encountered most frequently immediately, or very soon, after operation Occasionally a patient may remain well for several months and then suddenly become ill and develop an acidotic coma in a few days It is probable that these relapses are due to an exacerbation of renal infection.

Treatment

Prophylactic Alkalies and antibiotics are given during the post-operative period (e g. sodium bicarbonate 9 g /day and tetracycline) Plasma electrolyte estimations should be made at frequent intervals and potassium given if necessary. For the first few days a catheter is kept in the rectum to shorten the time during which the urine is in contact with the mucous membrane of the bowel Later the patient is advised to restrict the quantity of salt in his food and is given about 5 g of sodium bicarbonate to take per day, he is also told to allow the urine to escape from the rectum at frequent intervals.

Curative. If the patient subsequently complains of mild nausea, tiredness and headache, the administration of alkalies is increased (e g. sodium bicarbonate 3 g. eight-hourly), a low-salt diet is given, and a course of antibiotics should be given even if there is no overt evidence of renal infection.

When the symptoms are more severe and include vomiting, dehydration and clouding of consciousness, the rapid administration of

1/6 molar sodium lactate intravenously, together with 5 per cent. glucose will usually cause a quick return of consciousness. If the renal damage is reversible the blood urea will also quickly return to normal Antibiotics are again administered together with large quantities of sodium bicarbonate by mouth until the plasma bicarbonate is normal.

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19

RENAL CIRCULATION AND FUNCTION DURING AND AFTER ANÆSTHESIA AND SURGERY

ALMOST all forms of general anæsthesia produce a marked decrease in renal blood flow (Fig. 47). The onset of this decrease is rapid and its severity is related to the anæsthetic level; the flow remains lowered

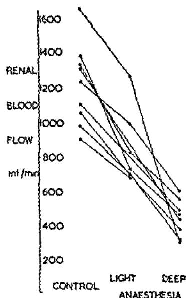


FIG 47. The effect of light and deep cyclopropane anæsthesia on the renal blood flow (After Miles *et al*, 1952, *Clin Sci*, 11)

throughout prolonged anæsthesia (Fig 48), and recovery from the anæsthesia is associated with a quick return to a normal flow This decrease in renal blood flow is due to a neurogenic renal vasoconstriction and is associated with a simultaneous and parallel fall in glomerular filtration rate.

The clinical significance of these changes is uncertain. At first sight they appear rather alarming but, on all occasions when renal blood flow measurements have been made, recovery has been so quick

and complete that it has been impossible to obtain any evidence to suggest that post-operative impairment in renal function is ever caused by the anæsthetic agent itself. Nevertheless, such observations have only been made on patients with normal kidneys and may not be relevant to patients with diseased kidneys. It is known, for instance, that after operation such patients often have a sharp rise in blood urea and may sometimes die of acute renal failure.

chronic renal disease, however, with a low glomerular filtration rate, the post-operative rise in blood urea will obviously be much greater,

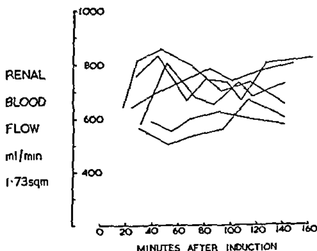


FIG. 48 The effect of prolonged cyclopropane and ether anæsthesia on the renal blood flow (After Lee *et al*, 1953, *Clin Sci*, 12)

particularly if there is a further fall in glomerular filtration rate (p. 23). If acute renal failure develops it is possible that the decrease in renal blood flow caused by the anæsthetic has been more prolonged and caused irreversible changes The likelihood of a severe post-operative impairment of renal function is greatest when the preoperative glomerular filtration rate is below 50 ml./min., i e. the blood urea is greater than 50 mg per cent If surgery is unavoidable in such patients it is best not to use a general anæsthetic; if this is not possible the level of the general anæsthesia should be kept very light.

Surgical Operations

Surgical operations surprisingly cause no change in renal blood flow. The variety of operations throughout which renal blood flow

measurements have been made is limited, but includes partial gastrectomy and cholecystectomy It has been found that following the diminution of renal blood flow caused by the anæsthesia, no further change occurs during the operation except possibly a slight increase. There are, however, certain manœuvres, such as vigorous traction on the large bowel, which induce a severe but transient renal vasoconstriction

The effect of *hæmorrhage* upon the renal circulation in anæsthetised patients undergoing surgery is less well known. It is probable that in man, if blood loss is rapid and exceeds 50 per cent of the blood volume, the changes which follow are similar to those observed in animal experiments, i e there is hypotension and an immediate and intense renal vasoconstriction Diagnostically, hæmorrhage of this size clearly presents no difficulty, for it is easily recognised and promptly treated It is the smaller hæmorrhage that is potentially more dangerous, for it may go unnoticed

It has been found in man that the loss of up to 1,500 ml of blood during a surgical operation under a general anæsthetic produces no persistent change in the renal blood flow, heart rate or blood pressure during the subsequent hour If the blood loss is very rapid, there may be small transient changes, but once bleeding is arrested there is a return to the levels found before hæmorrhage It follows that if the extent of blood loss during surgery is judged only by changes in heart rate and arterial pressure, a patient may be returned to the ward suffering from severe but unrecognised oligæmia The seriousness of this situation is that after 5–7 hours such a sustained oligæmia causes intense renal vasoconstriction; and it is aggravated by the fact that oligæmic patients are liable to have a steep fall in blood pressure on recovery from an anæsthetic A combination of severe renal vasoconstriction *and* hypotension, due to an insufficient replacement of blood during operation, is very probably one of the causes of post-operative acute renal failure, particularly in patients suffering from chronic renal disease

Induced Hypotension during Anæsthesia

Induced hypotension is sometimes used to limit bleeding during surgery, the blood pressure being lowered either by methonium drugs, thiophanium derivatives, spinal or extradural anæsthesia. Renal blood flow measurements have been made in young anæsthetised patients during the hypotension caused by methonium drugs, and it has been found that the renal blood flow is not affected by the fall in pressure (Fig. 49)

This constancy of the renal blood flow indicates that renal vaso-

dilatation occurs. Perhaps this is not particularly surprising considering that the blood pressure is lowered by a vasodilator, but the fact that the renal blood flow remains unchanged suggests that the renal circulatory autoregulating mechanism (p 73) is also concerned. It

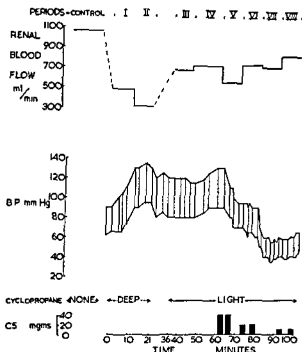


FIG 49 The effect of light and deep cyclopropane, and hypotension induced

if the systolic blood pressure is not allowed to fall below 80 mm. Hg, this contraindication may, in some circumstances, be disregarded. Such a moderate fall in blood pressure, induced by extradural anæsthesia, has been used with great success in prostatectomies for elderly patients with varying degrees of preoperative renal failure.

It is also potentially dangerous to lower the blood pressure in patients with severe atheroma of the main renal vessels, a condition that can *only* be diagnosed by an arteriogram. When the blood pressure falls the vessels will be unable to dilate and severe ischæmia

may result in postoperative renal failure Statistically this is a negligible risk, for it has been found in practice that the incidence of renal complications following the use of hypotensive techniques during anæsthesia is no higher than in a comparable control series.

Electrolyte and Water Excretion during and after Surgical Operations

During operation there is a sharp decrease in salt and water excretion The simultaneous fall in renal blood flow and glomerular filtration rate may be partly responsible, but it is probable that there is also a tubular effect, for morphia, anæsthesia and surgery all increase the level of circulating antidiuretic hormone, and the rate of urinary steroid excretion

Unlike the circulatory changes the decreased urinary excretion of salt and water continues for several days after operation and is accompanied by an increased excretion of potassium and nitrogen Oliguria lasts 24–36 hours and may be extremely severe , at this time the urine concentration is very high The decrease in sodium excretion lasts 3–6 days, and the increase in potassium excretion 1–2 days, while the increase in nitrogen excretion is variable

These changes are associated with an increased excretion of adrenal steroids It has been shown, however, that they are not dependent on a change in adrenal steroid output, for, if a patient is placed on a fixed dose of cortisone and then has a bilateral adrenalectomy, the post-operative changes in water, electrolyte, and nitrogen excretion are normal This is possibly due to the trauma of the operation causing a transient impairment in the ability to metabolise cortisone, so that the plasma concentration rises, or to the existence of other mechanisms which, though they are dependent on the presence of adrenal steroids, are able to alter independently

The proper recognition that after operation the 24-hour urinary volume and urinary chloride concentration are low, and the specific gravity is high, is of some importance, for it follows that during this time the urine volume and chloride concentration are no indication of the patient's salt and water balance In some patients the urine flow may be less than 200 ml /24 hours for the first day, and yet recovery is uneventful. Attempts to increase the urine volume and chloride excretion at such a time with large quantities of water or saline will only produce water intoxication or pulmonary oedema respectively The negative balance of potassium is of little importance, if the patient's stores of potassium are normal before operation But, in some cases, where there has been a prolonged preoperative loss of potassium (as in pyloric stenosis), the post-operative negative balance may be sufficient to cause clinical evidence of potassium deficiency.

Finally, it should be remembered that low volumes of urine should be highly concentrated A urine volume of 500 ml. a day should have a specific gravity of at least 1 018. If the specific gravity is lower, and particularly if it is approximately 1·010, it is an indication of tubular failure; frequently this is the first sign of post-operative tubular necrosis.

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20

"ALLERGIC" DISEASES OF THE KIDNEY

THE idea that the diseases included under this heading are due [illegible] histological features in common.

The following conditions are discussed.

(1) Glomerular nephritis.
(2) Renal disturbances in polyarteritis nodosa
(3) Renal disturbances in diffuse lupus erythematosus
(4) Renal disturbances in subacute bacterial endocarditis
(5) Renal disturbances in anaphylactoid purpura

GLOMERULAR NEPHRITIS

This disease consists of three clinical components.

CLINICAL COMPONENTS OF GLOMERULAR NEPHRITIS	RENAL SYNDROME AND ÆTIOLOGY
1 Acute glomerular nephritis	Acute nephritic syndrome (and very occasionally acute renal failure) due to an abnormal antigen-antibody response following an infection with β hæmolytic streptococci
2 Chronic glomerular nephritis	Chronic renal failure following either acute glomerular nephritis or persistent proteinuria of unknown cause, probably an abnormal antigen-antibody response.
3 Nephrotic glomerular nephritis	Nephrotic syndrome of unknown cause, probably an abnormal antigen-antibody response

Chronic glomerular nephritis may follow either of the other two forms, or may arise "spontaneously" The clinical course of each component of glomerular nephritis is illustrated in Fig. 50 Each has certain characteristic histological features, and in addition chronic glomerular nephritis tends to have some of the features of the form which has preceded it.

In the absence of a clear-cut common denominator it is not obvious

why these various renal disorders should be merged within one collective term. The reasons are histological, clinical and traditional.

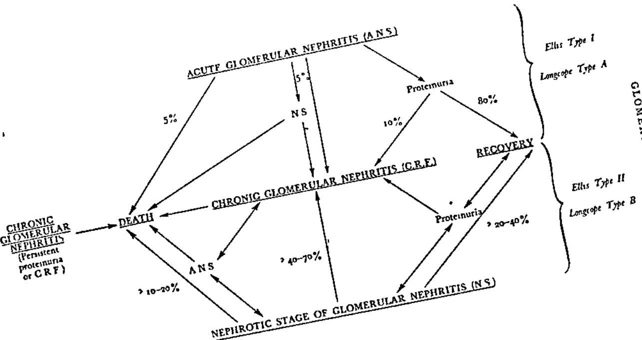
Histological The lesions in one patient may occasionally include some of the features of all three forms simultaneously; such cases discourage the tendency to consider them as separate entities

Clinical. The clinical reasons are shown in Fig 50 It shows that patients suffering from acute glomerular nephritis may develop a nephrotic syndrome, while others with nephrotic glomerular nephritis, or with chronic glomerular nephritis, may develop an acute nephritic syndrome Clinically, such cases defy subdivision and can only be placed under one comprehensive term

Traditional. It is traditional to group all those elements which now comprise glomerular nephritis since it was in this manner that they were originally described by Bright. His account is given below It is a descriptive compression of acute glomerular nephritis, the nephrotic stage of glomerular nephritis and chronic glomerular nephritis, as if they formed one continuous process. It is noticeable, however, that it is principally a description of acute glomerular nephritis developing into chronic glomerular nephritis; a nephrotic stage is only just discernible.

Bright's Description

"*A child or an adult, is affected with scarlatina, or some other* acute disease, or has indulged in the intemperate use of ardent spirits for a series of months or years he is exposed to some casual cause or habitual source of suppressed perspiration. he finds the secretion of his urine greatly increased [*sic*], or he discovers that it is tinged with blood, or, without having made any such observation, he awakes in the morning with his face swollen, or his ankles puffy, or his hands oedematous. If he happens, in this condition, to fall under the care of a practitioner who suspects the nature of his disease, it is found that already his urine contains a notable quantity of albumen: his pulse is full and hard, his skin dry, he has often headache, and sometimes a sense of weight or pain across the loins. Under treatment more or *less active, or sometimes without any treatment,* the more obvious and distressing of these symptoms disappear; the swelling, whether casual or constant, is no longer observed; the urine ceases to evince any admixture of red particles; and, according to the degree of importance which has been attached to these symptoms, they are gradually lost sight of, or are absolutely forgotten Nevertheless, from time to time the countenance becomes bloated; the skin is dry; headaches occur with unusual frequency; or the calls to micturition disturb the night's repose. After a time, the healthy colour of the



A N S. = Acute nephritic syndrome
C R F = Chronic renal failure
N S = Nephrotic syndrome

FIG 50 The three clinical forms of glomerular nephritis, their interconnection and prognosis

countenance fades; a sense of weakness or pain in the loins increases; headaches, often accompanied by vomiting, add greatly to the general want of comfort; and a sense of lassitude, of weariness, and of depression, gradually steal over the bodily and mental frame. Again the assistance of medicine is sought. If the nature of the disease is suspected, the urine is carefully tested; and found, in almost every trial, to contain albumen, while the quantity of urea is gradually diminishing. If in the attempt to give relief to the oppression of the system, blood is drawn, it is often buffed, or the serum is milky and opaque; and nice analysis will frequently detect a great deficiency of albumen, and sometimes manifest indications of the presence of urea. If the disease is not suspected, the liver, the stomach or the brain divide the care of the practitioner, sometimes drawing him away entirely from the more important seat of the disease. The swelling *increases and decreases; the mind grows cheerful* or *sad; the* secretions of the kidney or the skin are augmented or diminished, sometimes in alternate ratio, sometimes without apparent relation. Again the patient is restored to tolerable health; again he enters on his active duties, or he is, perhaps, less fortunate; the swelling increases, the urine becomes scanty, the powers of life seem to yield, the lungs become oedematous, and, in a state of asphyxia or coma, he sinks into [illegible] effusion of serum into the glottis closes the

to constant recurrence of his symptoms; or again, almost dismissing the recollection of his ailment, he is suddenly seized with an acute attack of pericarditis, or with a still more acute attack of peritonitis, which without renewed warning, deprives him in eight and forty hours, of his life. Should he escape this danger likewise, other perils await him; his headaches have been observed to become more frequent; his stomach more deranged, his vision indistinct; his hearing depraved: he is suddenly seized with a convulsive fit, and becomes blind. He struggles through the attack; but again and again it returns; and before a day or a week has elapsed, worn out by convulsions, or overwhelmed by coma, the painful history of his disease is closed"

To summarise, there is both clinical and histological evidence that the three different clinical forms of glomerular nephritis may be manifestations of at least two, or three, separate disease processes. Nevertheless they are often so intertwined that the inclusive term "glomerular nephritis" will continue to be necessary until more is known of their ætiology.

Acute Glomerular Nephritis

Ætiology

Infecting Organism. Acute glomerular nephritis follows infection with a β hæmolytic streptococcus, usually type 12, though a few other strains are occasionally involved This specificity of strain accounts for the irregular manner in which cases of acute glomerular nephritis appear. Until this was recognised, it was difficult to know why the incidence of acute glomerular nephritis varied so widely among epidemics of streptococcal infection particularly why several members of a family should suddenly develop the disease almost simultaneously

Abnormal Antigen-Antibody Response. It is clear that the organism does not produce its effect by its presence in the kidney, for it cannot be identified therein All the evidence points to a disturbed antigen-antibody response to the invading organism There is the delay between infection and the onset of nephritis, the abnormal and persistent rise in plasma antistreptolysin titre, and the lowered serum complement There is also a great deal of animal experimental work in which it has been shown that functional and histological lesions similar to those found in acute glomerular nephritis can be produced by the administration of foreign proteins or anti-kidney serum

Site of Infection. This is usually the throat or the skin Typically there is such a severe sore throat that the patient has to retire to bed for several days; in children scarlet fever was at one time a major cause of acute nephritis, but it is now less frequent, perhaps because of the use of penicillin The proportion of cases in whom it is possible to obtain a satisfactory history of previous infection is about the same in children as adults

Interval between Infection and the Onset of Acute Glomerular Nephritis. This interval varies from 2–3 days to more than a month, it averages 14 days It is usual for the patient to have returned to work or school before the onset of acute glomerular nephritis.

Sex and Age. Acute glomerular nephritis is more common in males, and is seen most often below the age of 20 years, however, it is by no means confined to this age group and is frequently seen at all ages, including the elderly

Pathology

Characteristically, the kidneys are normal in size, shape and colour, although occasionally there may be punctate hæmorrhages on the surface Microscopically the structural changes are principally in the glomeruli Often all glomeruli are equally affected, but frequently

the changes vary in intensity not only between one glomerulus and another but in different parts of the same glomerulus. There appears to be an increase in the number of the endothelial cells, but what is even more striking, they have a considerably greater quantity

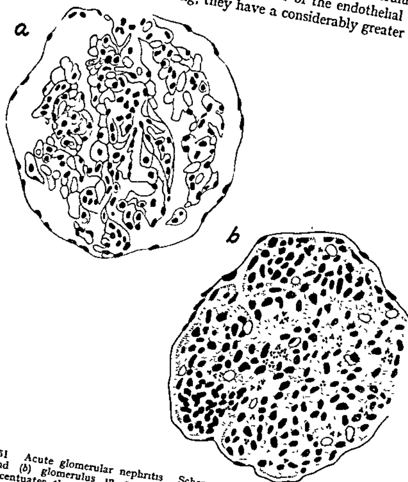


FIG 51 Acute glomerular nephritis Schema of (a) normal glomerulus, and (b) glomerulus in acute glomerular nephritis The diagram accentuates the following points the abnormal glomerulus is larger than normal, the glomerular tuft fills the capsule almost completely because it contains an increased number of cells with enlarged nuclei, there are focal collections of neutrophil polymorphs; and the capillary lumens are small, circular and lie near the periphery

of cytoplasm, and their nuclei are enlarged If this change is diffuse throughout a glomerulus it then loses its normal rather delicate tracery and instead appears stuffed with nuclei and cytoplasm (Fig 51) This is accentuated by swelling of the basement membrane, and the appearance of numerous fragmented collagen fibrils.

Renal biopsy material shows that the quantity of blood present in the capillaries is normal. Polymorphs are usually present in considerable numbers and are scattered unevenly in the tufts of those glomeruli which show the changes just described. Occasionally small foci of necrosis can be seen, and even intracapillary thromboses. The cells of the glomerular capsule sometimes enlarge, become cuboidal and histologically resemble the cells of the proximal tubule, the loose shredded cytoplasm of these capsular cells is sometimes thought to represent precipitated protein which has leaked through the damaged glomerulus. Proliferation of the capsular epithelium into crescents is unusual. Unequivocal evidence of inflammatory exudate in the capsular space is rarely seen.

In approximately half the cases, renal biopsies have shown the presence of focal areas of tubular degeneration. These are situated throughout the nephron, but are found most often in the distal tubules. A few patients have focal areas of complete tubular necrosis. Each site of tubular damage is surrounded by inflammatory cells, including lymphocytes, plasma cells, eosinophils and polymorphs. Occasionally, the most severe cases show a generalised separation of the tubules by a thickening of the interstitial tissue. In the interstitial spaces there are scattered, small collections of inflammatory cells and sometimes a glomerulus may be surrounded by a band of inflammatory cells including polymorphs, eosinophils and lymphocytes. Arteriolar necroses have occasionally been seen at post-mortem.

In some cases of acute glomerular nephritis without proteinuria or hæmaturia there are no structural changes except for the occasional presence of cuboidal capsular epithelium.

Clinical Features

The clinical features of acute glomerular nephritis are those of an acute nephritic syndrome (p. 142). Clinically the cardinal points are the sudden onset of oedema, gain in weight and oliguria; raised blood pressure and bradycardia, raised jugular venous pressure and dyspnœa, hæmaturia, proteinuria and discoloured urine. Acute glomerular nephritis is the commonest cause of heart failure in children.

Relationship Between Certain Clinical and Structural Features

Renal biopsy studies have shown that in acute glomerular nephritis the presence of proteinuria and hæmaturia is evidence of widespread and pronounced proliferative and inflammatory changes in th glomerular tufts, though the severity of these structural changes bea no relation to the extent of the proteinuria or hæmaturia. Surprising there is only an uncertain relationship between the creatinine cleara

and the structural changes in the glomeruli; and the concentration of the blood urea is the poorest guide to the presence or extent of such changes Impairment in the ability to concentrate is certain evidence of widespread focal degenerative lesions of the tubules, though these can be present without gross changes in concentrating ability, a raised erythrocyte sedimentation rate above 50 mm. in the first hour (Westergren) is highly suggestive of tubular degeneration.

Course

Fig 50 illustrates the eventual outcome of acute glomerular nephritis In about 80 per cent. of instances there is complete recovery; 5 per cent. die within one to two weeks of acute cardiac failure, acute renal failure or hypertensive encephalopathy, while the remainder develop chronic glomerular nephritis. The chronic stage may either develop as a rapid deterioration of the acute phase with increasing oedema and hypertension and death within a year (5 per cent.), or there may be almost complete recovery, except for the continued presence of proteinuria which persists for up to 25 years before the onset of chronic renal failure (10 per cent) A superimposed nephrotic syndrome occurs particularly in those who develop and die of chronic glomerular nephritis within a year.

Differential Diagnosis

The onset of acute glomerular nephritis is sometimes indistinguishable from that of several other conditions which give rise to an acute nephritic syndrome. The history of recent infection and the identification of the streptococcus are useful distinguishing points. Occasionally a patient may present with acute renal failure following the use of a sulphonamide for a streptococcal infection. It may then be extremely difficult to decide whether the patient has acute glomerular nephritis or acute tubular necrosis. In such cases it is essential that the ureters be catheterised to make certain that they are not plugged with crystals of sulphonamide and tubular débris (p 106).

The two conditions which cause most confusion are some cases of polyarteritis nodosa, and disseminated lupus erythematosus; often the correct diagnosis is only made retrospectively A pyrexia for longer than the first two to three days, or the continued presence of macroscopic hæmaturia are highly suggestive of a diagnosis of polyarteritis nodosa.

Prognosis

Acute renal failure is the complication most likely to destroy the patient in the first few days Acute glomerular nephritis is one of those

rare causes of acute renal failure in which there is complete cessation of urine flow Even if life is prolonged by appropriate measures, death almost always occurs Acute heart failure and hypertensive encephalopathy should respond to treatment.

Recurrent exacerbations of hæmaturia and hypertension, with violent fluctuations in glomerular filtration rate and blood urea, carry an increasing risk that the patient may rapidly develop chronic glomerular nephritis Nevertheless a guarded prognosis should be given for a considerable time, for recovery may take place even if the disease has persisted in this manner for several weeks

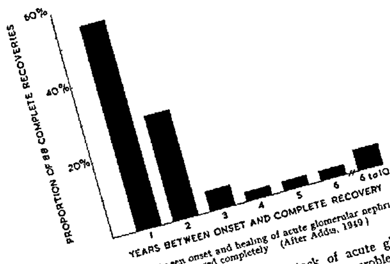


Fig 52 Interval between onset and healing of acute glomerular nephritis in 88 cases who recovered completely (After Addis, 1949)

The proteinuria which follows any attack of acute glomerular nephritis constitutes the most difficult prognostic problem It is generally considered that the patient has an active renal lesion until proteinuria ceases, and that the longer this continues the more likely it is that he will develop chronic glomerular nephritis and renal failure Complete recovery, therefore, has not taken place until proteinuria ceases But for how long may it continue and yet recovery occur? Fig 52, drawn from Addis's observations, gives the most comprehensive answer It can be seen that whereas in the majority proteinuria ceases within two years, there are some patients in whom it continues for six to ten years before it disappears The moral is to be optimistic

Treatment

Prophylactic It is reasonable to try and eradicate the β hæmolytic streptococcus from a small community (i e a family), in which a case of acute glomerular nephritis has occurred The organism is highly specific and easily removed by one injection of long-acting penicillin

Curative There is no known way of preventing acute glomerular nephritis developing into chronic glomerular nephritis Accordingly, treatment is directed solely at saving the patient's life and shortening the duration of the acute attack.

The site of the β hæmolytic *streptococcal infection should be* determined and if there is any reason to believe that the organisms are still present, i.e positive culture, soreness, redness or pus, a short course of penicillin should be given. Some authorities consider that penicillin should be given as a routine

Bed rest is essential, for it is remarkable how often a diuresis and recovery will begin within a few hours of the patient's retiring to bed, irrespective of the duration of the illness up to that time Rest in bed also diminishes the risk of left heart failure and hypertensive crises For the first 24 hours it is well to allow only 500 ml. of sweetened fruit juice by mouth and nothing else. This allows time to observe the direction the illness is taking and its severity. If during that time a diuresis has begun, i e if the urine volume is greater than 1,000 ml. and there has been a loss of weight, then a normal diet and unrestricted intake of fluids is allowed If a diuresis has not begun but the urine volume is greater than 400 ml , the intake of fluids for the next 24 hours should be limited to 500 ml plus a volume equal to that which has been passed in the preceding 24 hours, a low-salt, low-protein diet is also started. By these means it is hoped to prevent the onset of cardiac failure and to minimise the rise in blood urea. If the urine volume has been lower than 400 ml. the patient is considered to have acute renal failure and treated accordingly (p. 115).

The treatment of acute cardiac failure and hypertensive fits has been described on p. 146

Once a diuresis has begun there is no evidence that the speed of [illegible] of protein in the diet. [illegible] follow- [illegible] high or low protein diets are given for some weeks after the [illegible] and urea retention have ceased.

How long the patient should remain in bed once the oedema, the [illegible] hypertension and raised blood urea have [illegible] er of red cells or the amount of [illegible] routine Addis counts are being

estimated then progress is guided by the red cell excretion. The aim is to allow the patient to get up once the red cell excretion, *though still raised*, has reached a relative plateau. The excretory rate should have fallen to somewhere near 1,000,000/hr. Usually, however, progress is judged by the extent of the proteinuria, and again it should reach a steady level before the patient is allowed to get up. As a rough approximation, it should fall below 1 g./24 hours, or be no greater than + in a sample of urine with specific gravity above 1·016

It is clearly a useless and an unwarrantable interference with the patient's liberty to keep him in bed until proteinuria disappears, for (1) proteinuria will persist for over a year in about half of the 90 per cent of patients who eventually make a complete recovery (Fig 52), and (2) in those in whom the disease remains active it may persist for 25 years There is no evidence that the duration of rest in bed influences the eventual course of the disease

Chronic Glomerular Nephritis

Ætiology

Clinically, chronic glomerular nephritis either (1) follows an attack of acute glomerular nephritis in a clinically recognisable manner, or (2) it presents without any previous known history or evidence of renal disease In the first group it seems reasonable to venture that the development of chronic glomerular nephritis is related in some way to an abnormal antigen-antibody response to the β hæmolytic streptococcus, though there is no evidence of such an abnormality by the time chronic glomerular nephritis develops. The ætiology of the second group is even more uncertain

Pathology

The pathology of chronic glomerular nephritis is described under three headings, depending on its clinical antecedents (*a*) following soon after an attack of acute glomerular nephritis, (*b*) following some years after an attack of acute glomerular nephritis, or without any previous history of renal disease, or (*c*) following nephrotic glomerular nephritis

When chronic glomerular nephritis rapidly follows an attack of acute glomerular nephritis most of the features of acute glomerular nephritis remain In addition the glomeruli show patchy depositions of an eosin staining material which in some glomeruli completely replaces all cellular structures, turning them into homogeneous round pink blobs This substance is collagen, when it has replaced the glomerulus, it is itself absorbed and invaded by surrounding tissue cells and

eventually all trace of the glomerulus disappears. Many glomeruli show intense capsular hyperplasia with layers of reduplicated cells surrounding the glomerular tuft (i e. crescents) (Fig. 53). The glomeruli most affected are frequently surrounded by periglomerular fibrosis Nearly all the glomeruli are involved to a greater or lesser extent. The

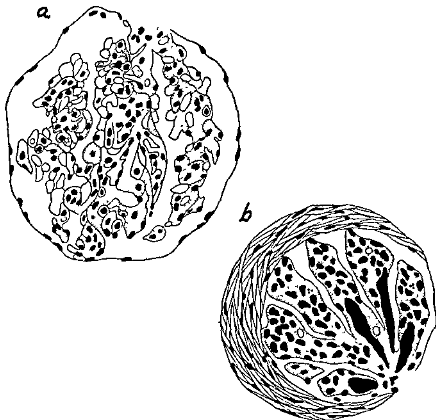


FIG 53 Chronic glomerular nephritis Schema of (a) normal glomerulus, [illegible] after ng t, ck ar ow capillary lumens are shown

tubules show irregular patches of atrophy and separation similar to those described below. Interstitial collections of inflammatory cells are numerous and are particularly dense around disintegrating glomeruli

The pathological appearances of chronic glomerular nephritis which

follows several years after an attack of acute glomerular nephritis, or which appears without a previous history of renal disease, are more advanced but less "active" than those just described Both kidneys are shrunken, irregular and firm, and the surface is pitted from contraction of underlying fibrous tissue, and raised by areas of hypertrophied nephrons.

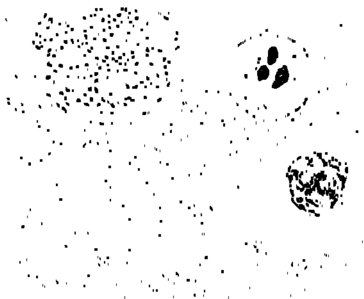


Fig 54 Schema of [illegible]

Microscopically, the most significant feature is that the normal structural layout of the kidney has been completely shattered (Fig 54) In acute glomerular nephritis, and in chronic glomerular nephritis following rapidly after acute glomerular nephritis, there are severe changes, but the kidney on section continues to look like a kidney After several years of nephron destruction it is hardly recognisable There is a large amount of fibrous tissue interspersed with nephrons which are either hypertrophied or in varying stages of disintegration.

One of the most striking features is the scarcity of glomeruli. Some of the remaining glomeruli show irregular proliferation of the tufts and of the capsule, and recent exacerbations of activity can be deduced by the extent of this cellular proliferation Sometimes all the changes of acute glomerular nephritis are found superimposed upon a background of advanced renal destruction from chronic glomerular nephritis

Most of the tubules which remain are insignificant, atrophic, and have flattened epithelium, and narrow lumens; they no longer lie in apposition to one another but are separated by an amorphous structureless material which in
nephrons are easily id
wide tubules (it is in
chronic renal failure originate) Between the nephrons there are also irregularly placed collections of chronic inflammatory cells, these are most numerous when the rate of renal destruction has been particularly rapid

When chronic glomerular nephritis follows nephrotic glomerular nephritis all the pathological changes described in the preceding section are present, though cellular proliferation in the glomeruli is unusual, and in addition there are the changes seen in the nephrotic stage

In the glomeruli these usually consist of the deposition of an eosin staining substance which is a mixture of collagen and basement membrane material The latter, unlike collagen, which is distributed in a haphazard manner in the glomerulus, is laid in the walls of the capillaries and gives them a smoothly thickened appearance. Eventually the whole glomerulus is replaced by these two substances and, as in the other forms of chronic glomerular nephritis, the glomerulus then appears as a round eosin staining structureless mass. Gradually the basement membrane material is replaced by collagen, then once again the collagen is absorbed and invaded by surrounding tissue cells and the glomerulus disappears This series of changes appears to take longer to complete than when only collagen is laid down, for there tend to be many more pink structureless glomeruli present throughout the kidney of a patient who has died of chronic glomerular nephritis following on the nephrotic stage than in one in whom it has followed acute glomerular nephritis some years previously. The other distinguishing feature of the nephrotic stage of glomerular nephritis is the appearance of vacuoles, and droplets of eosin staining material in the cells of the proximal tubules, the nature of this material is unknown; the vacuoles represent the spaces wherein fat was deposited

In all three varieties of chronic glomerular nephritis there may

be changes in the arteries; including atheroma, intimal and medial thickening, endarteritis obliterans, and arteriolar necroses These in turn will produce varying degrees of change in the renal parenchyma (p. 82), in addition to those just described.

Clinical Features

Chronic glomerular nephritis is characterised initially by persistent proteinuria and increased excretion of red cells and granular casts; later there is hypertension and chronic renal failure Sometimes persistent proteinuria with or without hypertension is found many years before the onset of chronic renal failure or hypertensive complications. Usually, however, the presenting symptoms are those of chronic renal failure (p 124) or hypertensive cardiac failure. Malignant hypertension occurs relatively often, as it does in many of the other conditions causing chronic renal failure

Course and Prognosis

The rate of renal destruction varies very greatly, it may fluctuate, with quiescent periods and acute exacerbations The duration of the disease, from beginning to end, may be as short as a few weeks or extend to 30 years but, once the glomerular filtration rate has begun to fall and the blood urea to rise, there is a tendency for the advance of chronic renal failure to be fairly rapid and inexorable. As a very rough approximation once the blood urea is greater than 50 mg. per cent the prognosis is not likely to be greater than 3–5 years, and over 100 mg per cent 1–2 years These figures relate to the concentration of blood urea when the patient is on an unrestricted diet, has not had a recent hæmorrhage or attack of diarrhœa and vomiting, is free from cardiac failure, and is not suffering from an acute exacerbation of the disease process as evidenced by the development of an acute nephritic syndrome or hæmaturia It has already been stressed repeatedly how circulatory insufficiency exacerbates renal failure and tends to give an erroneous impression of the extent of any underlying renal structural damage Such an exacerbation may cause death from acute renal failure at a time when there is only a moderate amount of renal structural damage

In general, the higher the blood pressure the poorer the prognosis The onset of malignant hypertension is nearly always fatal, for the sudden deterioration in renal function is usually too great to allow the blood pressure to be lowered without causing acute renal failure (p 74)

Differential Diagnosis

When the only evidence of renal disorder is persistent proteinuria

(orthostatic proteinuria having been excluded), and there is no history of previous renal disease, it is almost impossible to make a sure diagnosis of chronic glomerular nephritis A renal biopsy at this stage can be very helpful. Transient exacerbations of hæmaturia or of the acute nephritic syndrome make the clinical diagnosis more certain.

Once chronic renal failure occurs the condition has to be distinguished from the other causes of chronic renal failure (p. 124) It is important that there should be no confusion with chronic renal failure due to *chronic urinary obstruction*; the distinction is not particularly difficult.

The most common causes of confusion are chronic pyelonephritis, and nephrosclerosis (i e. renal destruction directly due to hypertension (p. 81).

In chronic pyelonephritis there are, in addition to persistent proteinuria, chronic renal failure and hypertension, the following signs and symptoms : (1) The urine contains organisms, though these may only appear intermittently, and in advanced chronic pyelonephritis the urine may always be sterile ; (2) there is a history of recurrent unexplained "chills," rigors and fevers, often with loin pain , (3) intravenous and retrograde pyelograms show deformities of the renal pelves, the characteristic feature of which are their bizarre shapes, and the way in which one side may be more severely affected than the other , (4) simultaneous, individual sampling from both ureters will also demonstrate unequal functional impairment ; (5) the urinary excretion of white cells is very large and usually greatly exceeds that of red cells In chronic glomerular nephritis the extent of the structural and functional disturbances is the same on the two sides, and the urinary excretion of red cells is much greater than that of white cells. Frequently none of these points of difference are present and, in these cases, a renal biopsy is sometimes useful.

Unless there are exacerbations of the acute nephritic syndrome or of hæmaturia, the distinction between chronic glomerular nephritis and nephrosclerosis is often impossible without a renal biopsy. The urinary deposit in nephrosclerosis is characteristically small and consists of approximately equal numbers of red and white cells, but this is a tenuous point on which to base a diagnosis. Statistically the more severe the renal failure the more certain the diagnosis of chronic glomerular nephritis becomes, for " non-malignant " hypertension only rarely causes advanced renal failure. Again, if a patient is found to have malignant hypertension and there is no previous history of renal disease, it may be impossible to determine whether there exists an underlying chronic structural lesion such as chronic glomerular nephritis. Malignant hypertension is more likely to be a complication

of pre-existing renal disease if the kidneys are small (straight X-ray of the abdomen, or I.V.P), or the renal failure is advanced when the diagnosis is first made.

Treatment

The treatment of chronic glomerular nephritis is that of chronic renal failure (p 134), the nephrotic syndrome (p 96), and the acute nephritic syndrome (p 145) It aims at minimising or controlling certain functional impairments. It is doubtful if any method slows the rate of renal structural disintegration, except possibly the control of hypertension

Nephrotic Glomerular Nephritis

Ætiology

This is unknown Similar functional and structural abnormalities can be induced in laboratory animals by a variety of experimental techniques which have as their common denominator an abnormal antigen-antibody reaction It is possible, therefore, that a similar mechanism is responsible for the disease in man The plasma anti-streptolysin titre in the nephrotic stage of glomerular nephritis is not usually raised, but the serum complement is sometimes below normal.

Pathology

The histological appearances are very variable In some no abnormality may be detectable, while in others the changes are severe , they may merge into those of chronic glomerular nephritis

Macroscopically the most characteristic changes are that both kidneys are pale, smooth and enlarged, and that the cut surface feels fatty

Microscopically, renal biopsy observations on early cases have shown that there may be no definite changes in the glomeruli The first disturbances are a focal thickening of the basement membrane and depositions of collagen, both the basement membrane and the collagen stain with eosin, but the basement membrane tends to be dense and uniformly coloured, while the collagen is pale and more irregular

At other times, there is a diffuse increase in basement membrane [illegible]

membrane and cell cytoplasm with special stains. In these cases the capillary lumens appear to be obliterated or greatly narrowed In other cases the basement membrane may show a compact thickening; capillary walls are dense, thick and sharp in outline, while the cellular

content of the glomerulus appears slightly reduced (Fig. 55) In biopsies these typical changes are only seen in about half the cases Often the uneven distribution of the basement membrane change, its intimate association with collagen, and an occasional focus of mild cellular hyperplasia, cause the appearances to be similar to those of the

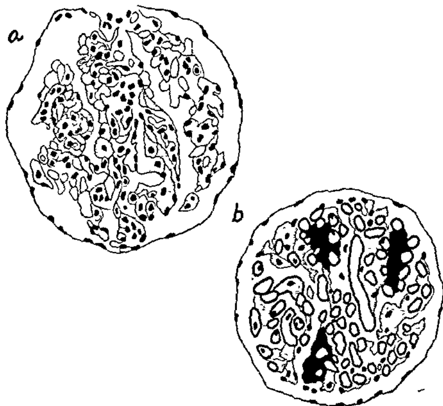


FIG. 55 Nephrotic stage of glomerular nephritis Schema of (*a*) normal glomerulus, and (*b*) glomerulus in the nephrotic stage of glomerular

early stages of lupus erythematosus, polyarteritis nodosa and chronic glomerular nephritis following acute glomerular nephritis. As the disease progresses the glomeruli become completely replaced by basement membrane material and collagen; their subsequent fate has been described above in the section on chronic glomerular nephritis (p. 194).

On the whole, the severity of the proteinuria bears no relation to any recognisable change in the glomerulus, but (1) occasionally a patient passing very large amounts of protein may show a foamy distension of some of the glomerular cells, as if they were distended with some fatty substance, and (2) within wide limits the quantity of protein excreted diminishes as the number of functioning glomeruli becomes less, i e, with a low glomerular filtration rate less protein is filtered and excreted

In some patients suffering from a nephrotic syndrome the tubules may show no abnormality. When tubular changes become manifest they are most marked in the proximal tubules; the cells are either flattened or distended with vacuoles and oval collections of a material which stains with eosin. If suitably prepared, the vacuoles can be shown to be filled with lipoids and neutral fat

There is much experimental evidence in animals that these intracellular tubular changes are related to proteinuria, but renal biopsy studies in man during the course of a nephrotic syndrome have shown that there is only a poor correlation between these changes and the severity and duration of proteinuria

As the disease progresses and nephrons are gradually destroyed, a number of atrophied tubules can be seen, separated by increasing quantities of interstitial substance which becomes the site of irregular collections of chronic inflammatory cells. The appearances gradually merge into those described in the section on chronic glomerular nephritis, including the hypertensive vascular changes

Clinical Features

Nephrotic glomerular nephritis can occur at any age, its clinical features have been described on p 94, where the nephrotic syndrome is discussed In addition there may be hypertension and renal functional impairment

Course and Prognosis

Before the introduction of antibiotics, secondary infections were the commonest cause of death, and the natural course of the disease was obscure Now that infection is a rare cause of death a clearer picture is emerging, but it will take several decades before an accurate appraisal is available Meanwhile it continues to be difficult to interpret published findings because of differences in terminology A diminishing number of authorities, particularly among those who look after children, consider that when a nephrotic syndrome is not associated with hæmaturia, hypertension, or a reduced glomerular filtration rate, it is a separate entity unrelated to glomerular nephritis,

and they distinguish it by the term "pure or genuine nephrosis" Today, however, it is generally considered that the available evidence does not justify such a distinction, and in these pages all such cases are included under the title "*nephrotic glomerular nephritis.*"

Some 30–50 per cent of cases will develop renal failure and/or hypertensive cardiac failure, and die within one to three years of the onset; about 20–50 per cent. will recover completely, perhaps after several remissions and relapses, and a few (? 5 per cent) will also have complete remission but will continue to have irregularly spaced relapses until proteinuria becomes permanent, when they join the group of 20–40 per cent. who continue to have oedema and proteinuria of varying severity for many years (up to 30 years) before developing renal failure and/or hypertensive cardiac failure Generalised oedema usually persists even when renal failure is advanced and proteinuria has diminished. Often an exacerbation or relapse of oedema and proteinuria is heralded by the onset of an acute nephritic syndrome. Complete recovery becomes less likely the longer the duration of the disease

As death is due either to renal failure or hypertension it is clear that as long as there is no evidence of either, the immediate and short term prognosis is good But even when these ominous signs do appear the prognosis is not necessarily poor, for sometimes, after an anxious few weeks, renal function may improve, hæmaturia cease, and the blood pressure return to normal Occasionally the glomerular filtration rate may remain around 40–60 ml /min. and the blood urea 50–70 mg. per cent. for many years (in one case up to 14 years). In some instances the blood pressure rises gradually but there is no marked deterioration in renal function

The earlier in the disease that hypertension and renal failure occur the worse the prognosis, particularly in children; it is also a bad sign when the extent of the oedema is massive and fails to respond to treatment

Differential Diagnosis

The other conditions in which the nephrotic syndrome may appear are given on p 91 Cases due to diabetes, anaphylactoid purpura or

of the renal vein is suspected if there is evidence of

thrombosis, recurrent pulmonary emboli from an unknown site, or the patient is known to have only one kidney.

There remain polyarteritis and disseminated lupus erythematosus (D.L.E.). Polyarteritis as a cause of the nephrotic syndrome is unusual; at the onset it may be very difficult to distinguish from glomerular nephritis even by renal biopsy. The diagnosis is made when some more characteristic features of polyarteritis nodosa become evident (peripheral neuritis, fever, tachycardia, muscle pains, etc.) and is confirmed by muscle biopsy. D.L.E. is the most difficult condition to distinguish from glomerular nephritis, for sometimes there are no firm clinical reasons for suspecting it and even renal biopsy findings may be equivocal. The only distinguishing feature may be the presence of L.E. cells in the peripheral blood or bone marrow.

Treatment

The treatment of nephrotic glomerular nephritis is symptomatic. It is mainly concerned with the elimination of oedema by a variety of methods, all of which have been discussed on p. 96.

It is probable that the continuous administration of adrenal steroids reduces the number of relapses, and retards the onset of renal failure and hypertension, but there is as yet little statistical evidence available. As relapses and remissions frequently follow infections, particularly those in the respiratory tract, reasonable attempts should be made to avoid these hazards, and when they occur they should be treated promptly and energetically with antibiotics

RENAL POLYARTERITIS NODOSA

This disease produces generalised disturbances (such as fever), and focal vascular lesions; in about 80 per cent of cases the kidneys are involved, either alone or in combination with other organs

[illegible]

responsible for the disease in man.

Pathology

The vascular lesions in the kidney may occur in the glomerular capillaries, the arterioles, or the small and medium sized arteries. The lesions are more scattered and difficult to find in the larger vessels; this is particularly relevant to renal biopsy material.

The characteristic glomerular lesion is a focal necrotising capillaritis in the midst of an acute inflammatory reaction; occasionally the entire

glomerulus is *necrosed* (*Fig. 56*). The arterioles may either show arteriolar necrosis with perivascular inflammatory cell reaction, or endarteritis obliterans (i e *the same lesions as in* malignant hypertension, except for the perivascular inflammation). The medium and small sized arteries show the diagnostic *lesion of polyarteritis* nodosa;



Fig

that is focal areas of acute segmental necrosis of a part or the whole of the arterial wall, *together* with an acute *inflammatory reaction* which invades and surrounds the necrotic area.

All these lesions occlude the lumen of the affected vessels and therefore the changes in the renal parenchyma (and the clinical features) largely depend on which vessels are *involved*. When the glomerular capillaries and the arterioles are affected *the glomeruli* will

show exudative and proliferative changes, like those seen in a case of acute glomerular nephritis rapidly deteriorating and developing chronic glomerular nephritis (p. 191).

When the small and medium sized arteries are affected there will be wedge-shaped areas of infarction in which the glomeruli will at first only appear "coagulated" or "clumped" and then become fibrosed and structureless, while the tubules, particularly the proximal tubules, become atrophied at an early stage; relatively normal renal tissue may surround the infarcts

Sometimes when the larger vessels are affected, the glomeruli may appear relatively normal but there are widespread tubular changes throughout the renal parenchyma, including tubular separation, changes in the nuclei, flattening of the tubular cells, and increase in size of their lumens It is possible that these lesions are due to partial occlusions of the arcuate arteries

When the vascular lesions heal there are focal areas of marked intimal fibrosis which contain capillaries (the sites of recanalised thrombi); focal ruptures of the internal elastic lamina, and areas of focal fibrosis of the arterial walls extending into the surrounding tissues.

Clinical Features

The wide variety of pathological changes accounts for the extensive range of clinical features Renal polyarteritis nodosa may present as acute renal failure, chronic renal failure, an acute nephritic syndrome, or a nephrotic syndrome, the predominant abnormality may be proteinuria or severe hæmaturia, or tubular inability to control electrolyte excretion The blood pressure tends to rise after the renal symptoms have appeared, and may continue to rise until there is malignant hypertension The disease is more common in men than women and is more easily diagnosed in the young than in the elderly.

Acute renal failure occurs if there are extensive necrotic lesions in the glomeruli, while proteinuria, chronic renal failure and severe hypertension are more likely if the lesions are in the small and medium sized arteries and there are multiple infarcts

One of the most frequent ways in which renal polyarteritis presents is as an acute nephritic syndrome For a few weeks the diagnosis is usually confused with acute glomerular nephritis, but eventually the slow rate of recovery, or the stormy course of the syndrome, together with the appearance of some other non-renal clinical feature of polyarteritis nodosa, suggests the proper diagnosis There may be attacks of severe unexplained central abdominal pain, fever, tachy-

glomerulus is necrosed (Fig. 56). The arterioles may either show arteriolar necrosis with perivascular inflammatory cell reaction, or endarteritis obliterans (i e. the same lesions as in malignant hypertension, except for the perivascular inflammation). The medium and small sized arteries show the diagnostic lesion of polyarteritis nodosa,



FIG 56 Polyarteritis nodosa Schema of two glomeruli, one (a) illustrates that the necrotic lesions may be focal while the other (b) shows that the whole glomerulus may become necrosed.

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in doubt; and the chance of finding such a lesion in the small amount of tissue removed by biopsy is remote The other renal histological features of polyarteritis may also appear in glomerular nephritis, lupus erythematosus, "embolic nephritis," malignant hypertension, and anaphylactoid purpura

A useful clinical point in difficult cases is the presence of fever, however mild it may be. If blood cultures are negative, there are no lupus erythematosus cells in the peripheral blood, and the urine is sterile, renal disease associated with a pyrexia is probably due to polyarteritis nodosa When polyarteritis is responsible for a nephrotic syndrome it is characteristic that the 24-hour urinary excretion of protein and the decrease in plasma proteins is more moderate than the extent of the oedema would suggest. Intermittent cardiac failure of uncertain origin and associated with only mild hypertension is another tenuous indication of polyarteritis.

Treatment

Adrenal steroids and ACTH are the only effective means of treatment They often produce a remarkable and immediate remission of the acute symptoms, and in some cases they indubitably prolong life. The dose should be large (e g. 40–60 mg prednisone per day), and it is essential that once a favourable effect has been produced the quantity should be continued uninterruptedly at the same high level If the dose of adrenal steroid is lowered rapidly there is often a relapse of symptoms, which for some inexplicable reason then no longer respond to adrenal steroids, or only do so when they are given in very large and potentially dangerous amounts (150 mg of prednisone per day) Treatment with adrenal steroids should be continued for at least a year, the dose being lowered very gradually at monthly intervals during that time (e g by 2–3 mg each month), if signs of activity persist treatment should be continued for longer

The complications of adrenal steroid therapy have been mentioned (p 98) The most important risk in the treatment of polyarteritis nodosa is retention and accumulation of salt and water, which may precipitate cardiac failure or a further rise in blood pressure. Initially therefore it is essential to measure the patient's weight and blood pressure and observe his jugular venous pressure each day If necessary salt and water retention can be controlled by restricting the salt intake, and if the blood pressure begins to rise, it should be lowered by hypotensive drugs The best of these are preparations of rauwolfia serpentina, which lower the pressure gradually and rarely cause a simultaneous fall in glomerular filtration rate, if this is unsuccessful, other drugs will have to be used (p 137). In some cases in which the

cardia, leucocytosis and eosinophilia, *peripheral neuritis, pulmonary* symptoms and radiological opacities in the lungs, skin rashes and nodules, or muscle pains and tenderness The most characteristic features of active renal polyarteritis are (1) recurrent, irregularly spaced, sharp attacks, of unremitting, unilateral loin pain of sudden onset, *usually lasting for less than* an hour, and followed by an increased rate of red cell excretion in the urine; these probably occur at the moment of, or shortly after, the formation of small *renal infarcts; occasionally* the pain radiates to, or may be situated entirely in, the flanks and front of the abdomen, and (2) long continued excretion of fluctuating quantities of *macroscopic* hæmaturia.

Finally the ability of the kidney to concentrate the urine is often *impaired to a far greater extent than is the glomerular filtration rate*

Course and Prognosis

Before the use of cortisone the majority of cases of renal polyarteritis nodosa died of renal failure or hypertensive cardiac failure within one to two years of the onset of the disease; the prognosis today is only a little better

The natural clinical course is often one of remissions and relapses, and occasionally evidence of such fluctuations can be found at autopsy, when both healed and active lesions of polyarteritis are seen. At any moment acute activity may cease Ultimate recovery then depends on the extent of the vascular lesions, for healed lesions may continue to produce harmful effects, such as malignant hypertension or chronic renal failure.

Death may occur from lesions in other sites, but renal failure is the commonest cause of death in polyarteritis Many cases develop renal failure fairly rapidly and die within a few months, those who begin with acute renal failure die within a few days.

Nevertheless some cases do recover; their number is not known, for unless there is *positive histological evidence the diagnosis is* uncertain, and it is obvious that such evidence is obtained less often in those patients who recover than in those who succumb

Differential Diagnosis

Syphilis used to be known as "the great imitator" *because of its* ability to mimic so many other diseases Now that advanced syphilis *is rarely seen*, this title might well be transferred to polyarteritis nodosa.

The renal disturbances caused by polyarteritis may suggest almost any form of renal disease. Unfortunately renal biopsy is not of much help in diagnosis, for unless a necrosed arteriole or artery *is seen*, surrounded by an intense inflammatory reaction, the diagnosis remains

in doubt, and the chance of finding such a lesion in the small amount of tissue removed by biopsy is remote The other renal histological features of polyarteritis may also appear in glomerular nephritis, lupus erythematosus, "embolic nephritis," malignant hypertension, and anaphylactoid purpura.

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blood pressure is very high at the onset it may be advisable for it to be lowered *before beginning* treatment with adrenal steroids.

RENAL LUPUS ERYTHEMATOSUS

Systematised lupus erythematosus resembles polyarteritis nodosa in that it also produces generalised disturbances and affects a wide variety of organs. The ætiology of lupus erythematosus is unknown; it is highly probable that it is another form of abnormal *antigen-antibody* response.

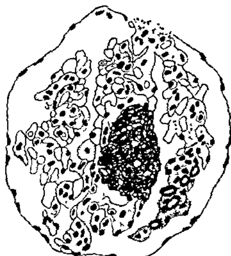


FIG 67 Disseminated lupus erythematosus Schema of a glomerulus in renal lupus erythematosus The diagram accentuates the focal nature of the lesions and that these consist of necrosis (in the centre), and cellular hyperplasia together with gross thickening of the walls of a few capillaries (both in the lower right quadrant)

Pathology

Renal biopsies have shown that the first renal lesions to appear in diffuse lupus erythematosus are (1) scattered small areas of local *endothelial proliferation of the glomerular tufts*, and (2) equally small areas of focal thickening of the capillary walls. As the disease advances cellular proliferation increases and there are focal patches of advanced degeneration in which "hæmatoxylin bodies" can be found These "bodies" are stated to be characteristic of *diffuse lupus* erythematosus and may represent breakdown products from the disintegrating nuclei; they appear as smudged hæmatoxylin staining areas of varying shapes and sizes, but they are considerably smaller than a nucleus.

In the acute terminal phase the changes in the *capillary walls*

become so marked that they have been referred to as "wire loop" lesions This term is misleading, for it contains the implication that the thickening of the capillary walls that occurs in renal lupus erythematosus is easily distinguished from that which occurs in other conditions, which is not true The thickening is due to non-specific changes which include (1) a granular disruption of the basement membrane, (2) an increase in basement membrane material, and (3) deposition of collagen The only features characteristic of lupus erythematosus are that the width and granularity of the capillary walls are occasionally very pronounced, and that these gross changes may be found in one part of the glomerulus, while the other parts are relatively normal (Fig 57) Even these vague distinctions, however, are becoming less useful, for after the administration of prednisone they occur much less frequently.

The other changes seen in lupus erythematosus are similar to those found in the nephrotic type of glomerular nephritis when it is deteriorating into chronic glomerular nephritis There is capsular proliferation, fibrosis of the glomeruli and tubular atrophy

Death from renal failure may take place before there has been much disintegration and absorption of nephrons In such cases the kidneys macroscopically are of normal size, or enlarged, while histologically there is a striking proliferation of both the glomerular capsule and the tufts, thickening and granularity of the capillary walls, exudates, hæmorrhages, and even necrosis in the tufts If, on the other hand, the changes have occurred more slowly, particularly when they have been retarded by prednisone, the kidneys will be smaller and the histological changes will resemble more closely those of chronic glomerular nephritis

Vascular changes may not be particularly pronounced, though sometimes the lesions of polyarteritis nodosa, or fibrinoid necrosis of arterioles, may be present

Clinical Features

Renal lupus erythematosus presents as proteinuria, a nephrotic syndrome, chronic renal failure or occasionally as an acute nephritic syndrome

Proteinuria and a nephrotic syndrome are the two most frequent presentations Usually the correct diagnosis is not made until some other more characteristic features of lupus erythematosus become manifest, e g skin lesions, fever, pleural effusion, pericarditis, arthritis, leucopenia, high erythrocyte sedimentation rate, and "L E" cells in the blood or bone marrow. Sometimes a patient may develop a nephrotic syndrome without a raised blood cholesterol.

By the time chronic renal failure occurs the diagnosis is usually less difficult It is characteristic that the blood pressure rises less frequently and much later than in other causes of renal failure, and that malignant hypertension is exceptional.

The disease is more common in women than in men.

Course and Prognosis

Disseminated lupus erythematosus is always fatal, death occurring sometimes in a few weeks. Death from renal failure occurs in 40–60 per cent. of all cases

Proteinuria shortens the prognosis and the onset of renal failure is followed by death within a year. Serial renal biopsies have shown that even when cortisone controls other manifestations of the disease, renal lesions continue to develop

When a nephrotic syndrome occurs without a rise in blood cholesterol, death follows in two to four months.

Differential Diagnosis

The two most diagnostic features of lupus erythematosus are the skin lesions and the presence of "L.E." cells in the blood and bone marrow. Without these it may be impossible to distinguish with certainty renal lupus erythematosus from the other causes of renal disorder.

The conditions most likely to be confused with renal lupus erythematosus are chronic pyelonephritis, renal polyarteritis nodosa and the nephrotic stage of glomerular nephritis

Treatment

The only treatment is the administration of ACTH, cortisone or prednisone in sufficient quantities to produce some relief of symptoms

RENAL DISTURBANCES IN SUB-ACUTE BACTERIAL ENDOCARDITIS

Renal disease due to sub-acute bacterial endocarditis is also called "embolic" nephritis, on the assumption that the disturbance is due to multiple renal emboli. There is, however, considerable doubt about this assumption, for:

1. The lesions are rarely seen until the infection has been present for at least six weeks
2. Bacteria are almost never found in the kidney.
3. When they are found it can be seen that the lesions they have provoked do not resemble the majority of the lesions which are present and which do not contain bacteria.

4 In some instances there are large numbers of lesions in the kidney, and few in other parts of the body.

5. The typical renal lesions can be produced experimentally as a feature of an abnormal antigen-antibody response.

6 Foreign particles injected into the circulation may embolise in the kidney but do not produce the characteristic lesions found in sub-acute bacterial endocarditis

These points suggest that the renal lesions in sub-acute bacterial endocarditis may be due principally to an abnormal antigen-antibody response to the organism responsible for the infection in the heart

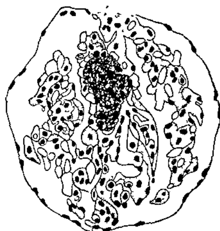


Fig 58 Sub-acute bacterial endocarditis (embolic nephritis) Schema of the characteristic focal necrotic lesion in a glomerulus.

Pathology

Macroscopically the kidney may appear normal, but if a considerable number of glomeruli are undergoing acute changes it may be swollen and covered with numerous petechial hæmorrhages, as in acute glomerular nephritis, malignant hypertension and diffuse lupus erythematosus

The characteristic microscopical lesion is an area of acute necrosis of a part (Fig 58) or the whole of a glomerulus, surrounded by varying quantities of acute inflammatory cells, and in the midst of which there may be intracapillary thrombi Occasionally there may also be arteriolar necrosis of afferent arterioles These lesions are usually scattered in widely separated glomeruli, but they are sometimes present in the majority. They are identical to the changes seen in the glomeruli and afferent arterioles in polyarteritis nodosa; the difference

By the time chronic renal failure occurs the diagnosis is usually less difficult. It is characteristic that the blood pressure rises less frequently and much later than in other causes of renal failure, and that malignant hypertension is exceptional

The disease is more common in women than in men.

Course and Prognosis

Disseminated lupus erythematosus is always fatal, death occurring sometimes in a few weeks. Death from renal failure occurs in 40–60 per cent of all cases.

Proteinuria shortens the prognosis and the onset of renal failure is followed by death within a year Serial renal biopsies have shown that even when cortisone controls other manifestations of the disease, renal lesions continue to develop

When a nephrotic syndrome occurs without a rise in blood cholesterol, death follows in two to four months

Differential Diagnosis

The two most diagnostic features of lupus erythematosus are the skin lesions and the presence of " L E." cells in the blood and bone marrow Without these it may be impossible to distinguish with certainty renal lupus erythematosus from the other causes of renal disorder

The conditions most likely to be confused with renal lupus erythematosus are chronic pyelonephritis, renal polyarteritis nodosa and the nephrotic stage of glomerular nephritis.

Treatment

The only treatment is the administration of ACTH, cortisone or prednisone in sufficient quantities to produce some relief of symptoms

RENAL DISTURBANCES IN SUB-ACUTE BACTERIAL ENDOCARDITIS

Renal disease due to sub-acute bacterial endocarditis is also called " embolic " nephritis, on the assumption that the disturbance is due to multiple renal emboli There is, however, considerable doubt about this assumption, for.

1. The lesions are rarely seen until the infection has been present for at least six weeks
2. Bacteria are almost never found in the kidney.
3. When they are found it can be seen that the lesions they have provoked do not resemble the majority of the lesions which are present and which do not contain bacteria

4. In some instances there are large numbers of lesions in the kidney, and few in other parts of the body.

5. The typical renal lesions can be produced experimentally as a feature of an abnormal antigen-antibody response.

6. Foreign particles injected into the circulation may embolise in the kidney but do not produce the characteristic lesions found in sub-acute bacterial endocarditis.

These points suggest that the renal lesions in sub-acute bacterial endocarditis may be due principally to an abnormal antigen-antibody response to the organism responsible for the infection in the heart.

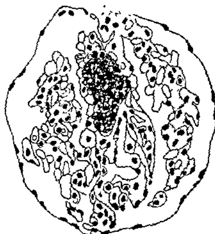


FIG 58 Sub-acute bacterial endocarditis (embolic nephritis) Schema of the characteristic focal necrotic lesion in a glomerulus

Pathology

Macroscopically the kidney may appear normal, but if a considerable number of glomeruli are undergoing acute changes it may be swollen and covered with numerous petechial hæmorrhages, as in acute glomerular nephritis, malignant hypertension and diffuse lupus erythematosus.

The characteristic microscopical lesion is an area of acute necrosis of a part (Fig. 58) or the whole of a glomerulus, surrounded by varying quantities of acute inflammatory cells, and in the midst of which there may be intracapillary thrombi. Occasionally there may also be arteriolar necrosis of afferent arterioles. These lesions are usually scattered in widely separated glomeruli, but they are sometimes present in the majority. They are identical to the changes seen in the glomeruli and afferent arterioles in polyarteritis nodosa, the difference

between the two conditions being that in bacterial endocarditis the small and medium-sized arteries are not affected

Following this acute stage the glomerular lesions become round structureless masses of eosin staining material and eventually become fibrosed. Characteristically these circular collections can be seen within otherwise normal glomeruli.

Patients who have died from renal failure usually show, in addition, the lesions of acute and chronic glomerular nephritis

Clinical Features

Frequently the patient is thought, or known to be suffering from sub-acute bacterial endocarditis, and routine examination of the urine shows occasional showers of red cells, or frank hæmaturia; such findings then help to establish the correct diagnosis.

Sometimes the diagnosis of endocarditis has not been considered or has been rejected because pyrexia and cardiac murmurs have been absent, or repeated blood cultures have been sterile In these patients *the significance of the proteinuria and the excretion of a few red cells* may not be properly appreciated. This occurs particularly in the elderly, who may then develop fatal renal failure.

In early cases treatment of the infection successfully prevents the further development of renal disturbances, but in cases with advanced renal failure such treatment is unlikely to save life

Diagnosis

A positive blood culture settles the diagnosis

When blood cultures are sterile, a renal biopsy may be helpful.

Treatment

This consists in identifying the organism, determining its sensitivity to various antibiotics, and then giving the appropriate one in suitable doses for a period of six weeks or longer, depending on whether blood cultures become sterile

RENAL DISTURBANCES IN ANAPHYLACTOID PURPURA

Anaphylactoid purpura (the Schonlein-Henoch syndrome) is characterised by a purpuric rash, abdominal pains, polyarthritis and hæmaturia; these usually occur in the young and follow a well-recognised infection such as tonsillitis, or occasionally they may be precipitated by the ingestion or administration of some substance to which the patient is subsequently found to be sensitive, e g. tomatoes.

The ætiology of this syndrome is considered to be an abnormal antigen-antibody response

Pathology

There are few observations of the histology of the kidney during life or after death; there does not appear to be any characteristic lesion. The appearances in advanced cases are the same as those found in acute glomerular nephritis which rapidly develop chronic glomerular nephritis. There is pronounced cellular proliferation in the glomeruli both of the tufts and the capsules, focal collections of chronic inflammatory cells in the interstitial tissues, particularly around abnormal glomeruli, and glomerular fibrosis and tubular atrophy.

Clinical Features

About 10–20 per cent. of all cases of anaphylactoid purpura have hæmaturia and proteinuria, and in addition an acute nephritic syndrome may also be present. In the majority of these cases there is subsequently a rapid and complete recovery, while a few continue to excrete protein and red cells. In most of these proteinuria may eventually disappear, but in the remainder it persists, chronic renal failure develops, and death occurs in one to five years. Recurrent attacks of macroscopical hæmaturia are a characteristic feature of this last group; they may also develop transient acute nephritic syndromes, and on rare occasions a nephrotic syndrome.

Approximately 10 per cent. of those who have hæmaturia and proteinuria at the onset of an attack of anaphylactoid purpura die of chronic renal failure subsequently.

Treatment

It is doubtful if any treatment influences the course of the renal lesions; nevertheless, it is reasonable in the acute attack to treat any residual infection with antibiotics. In some instances it may be necessary to give prophylactic penicillin when there are recurrent relapses due to β-hæmolytic streptococcal infections.

Treatment of the advanced renal disturbances is unrewarding, though occasionally a patient may respond dramatically to ACTH or adrenal steroids; there are even some reports of complete cure. Often, however, adrenal steroids only produce a rapid rise in blood pressure, jugular venous pressure and blood urea, and treatment must be discontinued.

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21

ORTHOSTATIC PROTEINURIA

THIS *benign condition is also called* postural proteinuria It consists of the excretion of protein in the urine only when the patient is in certain positions

Ætiology

Proteinuria can be produced in 75 per cent. of youths if they are placed in extreme lordosis, with increasing age the proportion gradually dwindles and, of men over 50, only 10 per cent will have proteinuria in this position

It has been demonstrated that in the lordotic position the liver in *these persons rotates forwards* and downwards and compresses the inferior vena cava. As a result there is a rise in the pressure within the inferior vena cava and renal veins, and protein appears in the urine

If, however, the patient stands in the lordotic position but the liver is prevented from sliding forward by firm digital restraint under the *right costal margin, the inferior vena caval pressure does not rise and* there is no proteinuria In bed, the lordosis of the upright position disappears and again there is no proteinuria, though it can be made to reappear by purposely assuming the lordotic position. Conversely, proteinuria will not appear in the upright posture if the patient remains *bent forward*

Renal Function

Excluding the proteinuria renal function is normal

Clinical Features

Orthostatic proteinuria occurs most frequently in children, adolescents and young adults It has been reported in 12–40 per cent. of children aged *10–16* years; and it *is claimed that this proportion is* greater if the urine is examined at frequent intervals. Orthostatic proteinuria occurs in about 5 per cent. of young adults.

The presence of protein in the urine is usually detected during a routine examination on going to school or university, or on entering the services. *Occasionally it is noted* as an incidental finding during an illness which is unrelated to the kidney. If many urine samples are

tested it is found that protein is present throughout the day, except in the first sample passed in the morning The concentration of protein rarely exceeds ++ and is usually + or less; the daily excretion is seldom more than 2–3 g. It is not unusual to find protein on some days and not on others Orthostatic proteinuria is of no importance; it does not influence the patient's health or the functional capacity of his kidneys. The majority of patients lose their proteinuria as they become older though it may continue for 10–30 years.

For routine purposes orthostatic proteinuria is distinguished from persistent proteinuria by asking the patient to empty his bladder just before going to bed, and to keep for examination the urine he passes next morning immediately he gets up This test can be combined with a 16- to 24-hour fluid deprivation test, when the ability to concentrate can be tested simultaneously

Differential Diagnosis

If proteinuria can be made to disappear with a change in posture it is almost certain that there is no renal disease. Nevertheless it is also characteristic of the proteinuria of renal disease that it is greater when the patient is up and about, and diminishes upon lying down On very rare occasions the proteinuria of renal disease may be altogether absent from the urine formed during the night, when it is then indistinguishable from benign orthostatic proteinuria These confusing cases usually declare themselves eventually; sometimes they can be differentiated earlier by an examination of the urinary deposit.

The presence of orthostatic proteinuria should therefore not be dismissed too lightly, particularly when it occurs in a patient over 30 years old.

Treatment

No treatment is necessary

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22

RENAL INFECTIONS

INFECTIONS of the kidney can be divided into those due to the tubercle bacillus and those due to other organisms; only the latter are described below As renal tuberculosis is usually considered to be a " surgical " disease it is not discussed here.

The following conditions will be considered: (1) Acute pyelonephritis, including acute pyelitis and acute necrotising papillitis; (2) Chronic pyelonephritis, including healed pyelonephritis.

ACUTE PYELONEPHRITIS

Including Acute Pyelitis and Acute Necrotising Papillitis

Ætiology

A wide variety of organisms may cause pyelonephritis; those found most frequently are *Escherichia coli, Klebsiella pneumoniæ, Pseudomonas pyocanea, Staphylococcus aureus, Proteus vulgaris* and *Streptococcus fæcalis*

The majority of infections are associated with obstructions of the urinary tract, these cause a rise in pressure, and possibly a slowing in the rate of urine flow in those parts which lie proximal to the obstruction About a third of infections, however, occur in kidneys with normal urinary tracts, nearly always in women A few infections occur during a widespread and easily recognised dissemination of organisms from a primary focus, such as malignant endocarditis, osteomyelitis, empyema, etc , the renal lesion thus caused is sometimes known as a " pyæmic kidney " but, as it is indistinguishable from severe acute pyelonephritis from other causes, it is included here.

Lesions which obstruct the urinary tract include certain abnormalities of the renal parenchyma which deform the calyces, such as hypoplasia, polycystic kidneys, and scarring from previous infections (including tuberculosis). Other causes are congenital abnormalities of [illegible] ureter and urethra; aberrant renal arteries; renal and ureteric [illegible] rs "; pelvic tumours; [illegible] Calculi and pregnancy are the two most frequent causes.

Infections frequently complicate other parenchymal renal diseases; for instance, acute pyelonephritis may develop in a patient known to be suffering from renal polyarteritis nodosa

The infecting organism may be conveyed to the kidney in (1) the blood stream, (2) the urine, from the bladder up the lumen of the ureters, or (3) the lymphatics alongside the ureters It is reasonable to suppose that when pyelonephritis follows a lower urinary tract infection (i e. cystitis) the organisms have ascended to the kidney via the ureters; but that otherwise they are blood-borne In this connection it is interesting to note that animal experiments have shown that the intravenous administration of large numbers of Gram-negative organisms only causes acute pyelonephritis if the ureters are temporarily occluded or the kidneys are already scarred from previous infections, whereas the administration of *Staph aureus* causes acute pyelonephritis even in normal kidneys

Linnæan and other Names of some of the Organisms which cause Urinary Infections *

LINNÆAN NAME	OTHER NAMES	COMMENT
Escherichia coli	B coli	The most frequent cause of acute urinary infections
Staphylococcus aureus	Staph pyogenes	Second most frequent cause of acute urinary infections
Klebsiella pneumoniæ	Friedlander's bacillus Ærobacter ærogenes	Usually in mixed infections and when there are structural deformities of the urinary tract Frequently after antibiotic therapy and indwelling catheter
Pseudomonas pyocyanea	B pyocyaneus Ps æruginosa	
Proteus vulgaris	B proteus	
Streptococcus fæcalis	Enterococci	Often follows catheterisation in women
Hæmophilus influenzæ	B influenzæ Pfeiffer's bacillus	Rarely found

* Hare, R (1956) An Outline of Bacteriology and Immunity Longmans, Green & Co, London

Examination of the Urine for Evidence of Acute Infection

The most reliable information is obtained from a microscopical examination of a *freshly collected* and *unsedimented urine* In an acute infection large numbers of white cells can be seen, and Gram staining shows many organisms When the urine is heavily infected it has a characteristic opalescent turbidity which does not disappear with dilution, heating, or the addition of acetic acid If the organisms change the urine urea into ammonia the fresh urine will have an

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scopically the kidneys are usually enlarged and occasionally small abscesses show through the capsule The surface may be discoloured by areas of pallor and congestion On section, greyish wedge-shaped areas can be seen extending upwards from the pyramids into the cortex; there are also yellow streaks radiating from the medulla The pelvis is red and covered with pus

The pelvis microscopically is covered with an inflammatory exudate which penetrates within the pelvic wall; sometimes there are also areas of superficial necrosis The renal parenchymatous lesions are predominantly in the pyramids and medulla. The tubules contain and are surrounded by leucocytes, though occasionally these are confined to the interstitial tissues There are similar collections of neutrophils in the interstitial tissues of the cortex but, in addition, some glomeruli become selectively invested by a thick concentration of acute inflammatory cells In a few, the capsule is breached and leucocytes can be seen invading the glomerular space In some sites an inflammatory destruction of tubules may cause a crowding together of glomeruli which are then separated only by granulation tissue A varying number of small abscesses may be disseminated throughout the renal parenchyma and, before the use of antibiotics, bacteria were also found in large numbers

The vascular lesions are of particular importance, and in this connection it should be recalled that the renal pelvis extends as far upwards as the cortico-medullary junction (p 5) It is not surprising, therefore, to find that sometimes the acute inflammatory process involves some of the larger arteries and veins Dense infiltrations with leucocytes may be localised in the arterial wall, leading to destruction of the muscle and elastic tissues, occasionally this process leads to occlusion of the lumen by a thrombus, and complete infarction of wedge-shaped areas of cortex Other large arteries may show moderate degrees of narrowing of the arterial lumen by endarteritis. In the areas of acute inflammation thrombosis of arterioles is relatively frequent.

Acute Necrotising Papillitis This consists of an acute pyelonephritis of such severity that there is a focal suppurative necrosis of several renal pyramids The process begins at the apices of the pyramids and extends upwards into the medulla, but does not involve the cortex Microscopically there is a dense purulent exudate throughout the affected area which is sharply demarcated from the viable parenchyma

Clinical Features

The onset of acute pyelitis and pyelonephritis are identical, the signs and symptoms are those of an acute upper urinary infection There is a sudden onset of fever, pallor and rigors, with pain and

offensive and distinctive smell. These signs are related to the numbers of organisms present and are most evident when the rate of urine flow is reduced and the bladder emptied at infrequent intervals, for the organisms multiply in the bladder.

A culture of the urine defines the organism responsible for the infection and permits its sensitivity to various antibiotics to be established In women, a catheter sample, and in men a mid-stream sample of urine is cultured As a diagnostic procedure urine culture is less satisfactory than a microscopical examination Apart from the inevitable delay, it has been found that only 25 per cent. of urine samples obtained from normal subjects are sterile, while the remainder contain varying numbers of organisms. It is probable that the positive cultures are mainly due to urethral contamination, for, if urine is obtained directly from the bladder with a needle and syringe during an abdominal operation, it is usually sterile. It is imperative that both the microscopical examination of the urine, and its plating for culture, should be performed as quickly as possible after collection. If the urine has been allowed to stand about in the ward or on the laboratory bench it is liable to give misleading information, for in the interval contaminating organisms will have proliferated and white cells disintegrated.

A heavy growth from freshly collected urine is a definite indication of acute or chronic urinary infection. If there are only a few colonies they may be due to chronic infection or contamination; it is suggestive evidence against an acute infection At the onset of an acute urinary infection it is sometimes possible to grow numerous organisms before there is any detectable increase in the number of white cells, even when a sedimented sample is examined

Pathology

The appearances of the kidneys depend largely on whether any underlying renal deformity was present before the onset of the acute infection The following descriptions only refer to changes produced by infection. They are divided into three groups depending on their severity (1) Acute pyelitis; (2) acute pyelonephritis; and (3) acute necrotising papillitis.

Acute Pyelitis This is the term which pathologists give to an acute inflammation confined to the lining membrane of the renal pelvis, that is an infection which does not involve the renal parenchyma. At post-mortem such a limited distribution is found extremely rarely; it does not follow that it is equally infrequent in life. It is usually bilateral

Acute Pyelonephritis. This may be unilateral or bilateral. Macro-

Prognosis

An acute infection of the renal parenchyma may cause death, either if it is sufficiently extensive, or if it is superimposed upon pre-existing chronic renal disease (e g. chronic pyelonephritis)

Once the acute infection has been controlled, the risk of further attacks and the development of chronic pyelonephritis depends largely on whether or not there is permanent deformity of the renal tract. Usually such deformities precede infections, but the changes produced in the renal parenchyma and pelvis by sufficiently severe or recurrent infections may themselves perpetuate the tendency to infection and the development of chronic pyelonephritis

It is essential to remember that a patient suffering from advanced renal failure secondary to an acute renal infection may rapidly recover once the infection is controlled, it is unwise, therefore, to volunteer a prognosis during the acute phase of the infection

Differential Diagnosis

Fever, rigors, tenderness and pain in one or both loins suggest, and the finding of pus and organisms in the urine confirm the diagnosis. Occasionally when local symptoms and signs are absent, the diagnosis only becomes apparent after a routine examination and culture of the urine *An acute urinary infection should always be kept in mind when the patient is known to suffer from some other chronic parenchymal renal disease*

It has recently been shown, by culturing organisms from renal biopsy material, that parenchymatous renal infections may occur without organisms appearing in the urine The frequency of this condition is not known, the cases described had pyrexia of unknown origin, proteinuria and some mild impairment of renal function

Treatment

There are three guiding principles (1) The control of the acute infection, (2) investigation of any underlying renal or urinary tract abnormality, and (3) the prevention of further attacks

Control of the Acute Infection. Patients used to recover from acute upper urinary infections before the arrival of antibiotics It is probably true, therefore, that many superficial infections of the renal pelvis (e g pyelitis) would recover if treatment were limited to the administration of large quantities of water and potassium citrate Clinically, however, it is impossible to be certain when an infection is confined to the pelvis, and in practice it is best to give an antibiotic in all upper urinary infections, for if the inflammatory process has penetrated into

tenderness in the loins and the flanks, and the presence in the urine of large numbers of white cells and bacteria; proteinuria is rarely greater than a "trace" to +. Frequently there is much nausea and vomiting, and with severe attacks there may be gross macroscopical hæmaturia. If there is a simultaneous lower urinary infection there will also be frequency of micturition, dysuria and lower abdominal pain and tenderness. The clinical features give no clue to the identity of the infecting organism.

Even before the introduction of antibiotics most patients presenting with these symptoms recovered, and it is therefore improbable that the pathological changes which have been described above as those of acute pyelonephritis occur at all frequently. It is more likely that most upper urinary infections are limited to an acute pyelitis. Nevertheless, as it is clinically difficult, particularly at the onset, to differentiate between the two conditions it is best to consider that all upper urinary infections involve the renal parenchyma, i.e that all such infections may be associated with acute pyelonephritis

The extent of the parenchymatous involvement depends mainly on the presence of urinary tract obstruction; the greater the obstruction the more extensive the infection Such obstructions are often found in patients of either sex who have recurrent infection; they underlie most upper urinary infections that occur in men, whereas women frequently have recurrent infections without any abnormality of the urinary tract, in such instances the organisms probably enter the bladder via the urethra and ascend to the kidneys up the ureters

Renal function in upper urinary infections may be unaffected (presumably when the infection is confined to the pelvis), but in acute pyelonephritis it may be so severely impaired that the patient dies from acute renal failure Characteristically renal function returns to its previous level as the infection subsides. The magnitude of this transient impairment is probably of some value in assessing the amount of parenchyma that has been invaded by the acute inflammatory process Proper appraisal may be difficult if some degree of renal failure preceded the infection; at such times renal function should be re-examined a few weeks after the infection has been controlled.

Acute Necrotising Papillitis. This occurs most often in elderly diabetics, most of whom have suffered from previous upper urinary infections In addition to the usual features of a severe acute upper urinary infection, hæmaturia occurs frequently and, if the lesion is bilateral, there is a sudden reduction in urine flow, and the onset of acute renal failure. Sometimes pieces of necrosed papillæ appear in the urine If the patient recovers, the loss of part of one or more papillæ may be defined in an I V.P or retrograde pyelogram.

ANTIBIOTICS USED TO TREAT URINARY INFECTIONS

Antibiotic	*Dose*	*Methods of Administration*	*Comment*
Sulphadimidine (Sulphamezathine)	3 g loading dose 1 g 6 hourly	Oral administration—intramuscular and intravenous preparations available	Particularly useful in acute infections * Emphasise need to drink much fluid
Tetracycline	0 25 g 6-hourly	Oral administration—intramuscular and intravenous preparations available	Wide spectrum—the most useful antibiotic in the treatment of urinary infections *
Nitrofurantoin (Furadantin)	0 1 to 0 15 g 6 hourly	Oral—after meals preferably Intravenous preparation available	Wide spectrum—particularly useful against *B proteus* infections. Nausea often with more than 400 mg a day *
Methenamine mandelate . (Mandelamine)	1 to 2 g 8-hourly	Oral only Urine must be acid Give ammonium chloride for first few days	The least toxic urinary antiseptic—useful for *B coli*, *Staph aureus* and *Strep fæcalis* infections *
Erythromycin	0 2 g 4 to 6-hourly	Oral administration Intravenous preparation available	Useful against resistant *Staph aureus*, *Strep fæcalis* infections With other organisms often controls symptoms and pus content of urine without destroying the organism *
Penicillin	300,000 units 8-hourly	Intramuscular Oral preparations available	For *Staph aureus* infections
Streptomycin	1 g twice a day for 3 days, or 1 g a day for 10 days	Intramuscular Best effect if urine alkaline *Give potassium citrate 2 g* 6-hourly.	Useful against organisms resistant to other antibiotics particularly recurrent infections Best used as a short, heavy attack on the infection before beginning continuous therapy with some other drug Adjust dose to G F R
Novobiocin	0 5 g twice a day for 7–10 days	Oral or by intramuscular injection	Sensitivity reactions on 5–7th day very *commor* Measles-like rash, nausea and diarrhœa For resistant *Staph. aureus*, *Proteus*, *Strep fæcalis* infections
Polymyxin B	250,000 units 4-hourly for 2–3 days	Intramuscular into alternate buttocks	For *Pseudomonas pyocyaneus* infections
Chloramphenicol (Chloromycetin)	0 5 g 6-hourly for a few days only	Oral and intramuscular	Occasional irreversible aplastic anæmia * Only used when infecting organism resistant to all other drugs

* *These antibiotics can be used for 10–20 days in the treatment of an acute infection, or alternated at weekly intervals for continuous* therapy

the renal parenchyma it is reasonable to suppose that quick control of the infection will lessen the residual damage.

Sulphonamides are usually administered without first identifying the organism responsible for the infection. The repeated success of this blind manœuvre ensures its continuity, but there is no doubt that it is more satisfactory to culture the urine and determine the sensitivity of the organism. When there are recurrent infections it is imperative that this be done Antibiotics are excreted in the urine at varying rates, but in all instances their urinary concentration is greater than their simultaneous concentration in body fluids. For this reason, when the only purpose of treatment is to sterilise the urine, e g. in lower urinary infections, the administration of small quantities is sufficient. Such small quantities, however, are not satisfactory for upper urinary infections, for if the renal parenchyma is involved, organisms will be present in the interstitial spaces between the tubules, out of reach of the high concentrations within the tubules. The rational way to dispose of these organisms is to raise the concentration of antibiotics in the body fluids to that found necessary for the treatment of infections in other tissues. The administration of antibiotics should be continued for at least 10 days, and certainly *for some days after all traces of tenderness in the loins has disappeared*

When there has been evidence of extensive parenchymal invasion, that is, if renal function has been depressed by the infection, it is advisable to continue treatment for two to three months. Thereafter the urine should be cultured at intervals for at least a year, and urinary excretion of white cells should be determined from time to time (When urine for culture is obtained with a catheter, it is probably advisable, afterwards, to give a prophylactic dose of an antibiotic)

The choice of antibiotic is determined by the sensitivity of the infecting organism, but if the diagnosis is clear cut it is unnecessary to wait 24 hours for the result of urine culture; treatment is started with either sulphadimidine (3 g followed by 1 g 6-hourly) or tetracycline (0 25 g 6-hourly) immediately after some urine has been obtained for culture In this way no time will have been lost, whatever the result of culture. Other antibiotics are listed in the Table opposite

Investigation of Underlying Urinary Tract Abnormality. The structural integrity of the kidneys and of the urinary tract should be investigated following (1) any upper urinary infection occurring in a boy or a man, (2) a second infection in a woman, (3) a first infection in a woman if it is accompanied by renal colic, hæmaturia, impaired renal function, or followed by persistent proteinuria or large numbers of white cells in the urine. Intravenous and retrograde pyelograms

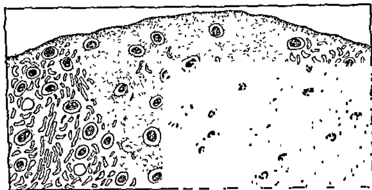


FIG. 69. Chronic pyelonephritis Schema of the cut surface of the kidney showing a characteristic wedge-shaped lesion

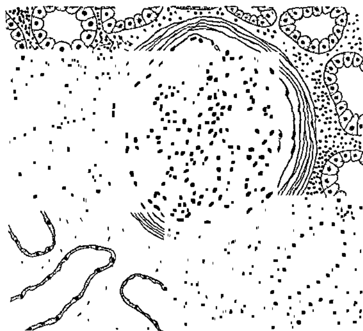


FIG [illegible]

containing casts are not shown)

are usually sufficient, though occasionally arteriograms and even laparotomy may be needed.

Prevention of Further Attacks. *The prevention of* recurrences is often a surgical procedure, with the repair or removal of structural deformity. Otherwise some form of prophylactic treatment may be necessary. This can consist of either small daily doses or large intermittent courses of antibiotics Sometimes it may even be necessary to give large doses continuously; this is particularly relevant to upper urinary infections in children. Occasionally a woman may have recurrent infections and yet have no detectable renal or urinary tract abnormality. Such attacks often follow or accompany lower urinary tract infections and develop shortly after sexual intercourse. They can sometimes be prevented by taking 1 g. of sulphadimidine or 0·25 g of tetracycline after intercourse

CHRONIC PYELONEPHRITIS

***Pathology* ***

The kidneys are small, coarsely and irregularly misshapen by scars and areas of hyperplasia of widely differing dimensions The extent of the damage is often more pronounced on one side than on the other and is sometimes entirely unilateral. The cut surfaces show scars extending from the pelvis to the capsule.

The characteristic microscopical appearances consist of patches of intense infiltration with lymphocytes and plasma cells (Fig 59); these areas are distributed in a haphazard manner, but concentrated more in the medulla than in the cortex The tubules in these sites are either small and atrophic, or dilated with flattened epithelium and contain [illegible] staining material The glomeruli [illegible] les; some may [illegible] ts, though they are surrounded by a thick collar of fibrous tissue (Fig 60); the remainder, however, show varying degrees of change in the tufts, including fibrosis and atrophy.

Frequently the changes of acute pyelonephritis are found interspersed and *superimposed upon those of chronic pyelonephritis*

The scarring is principally due to wedge-shaped areas of inflam- [illegible] been infected

they only last a few hours and disturb the patient very little. Inter- [illegible] but it is not often that they are sufficiently pronounced to cause comment Many patients will admit to intermittent spells of tiredness, headache and loss of appetite.

Characteristically, the urine contains (1) protein, but it is seldom excreted at a rate greater than 5 g per 24 hours; (2) large numbers of white cells, and (3) the same infecting organisms as those found in acute pyelonephritis. If a routine examination of the urinary deposit fails to show an increased number of white cells, an Addis count should be performed (p 29) It is possible for the urinary sediment to appear normal and yet an Addis count to show such an increase in white cell excretion that a diagnosis of chronic pyelonephritis can be made with relative certainty. The chances of obtaining a positive culture vary, and tend to diminish as the disease advances , in some cases no organisms are ever found. When urine cultures and white cell excretion rates are equivocal or normal and yet a chronic urinary infection seems very likely, it is sometimes possible to clarify the diagnosis by the intravenous injection of a pyrogen This produces an acute renal hyperæmia for several hours, and a day or two later a smouldering renal infection may suddenly flare up with fever, loin pain, raised white cell excretion and organisms in the urine

In general, renal functional impairment follows the same pattern as that described in the section on chronic renal failure (p 124), but there tend to be certain divergences, particularly in the early stages, which may be useful in establishing the diagnosis For instance, tubular function is apt to deteriorate more rapidly than glomerular filtration rate, so that it is not unusual to find an inability to concentrate the urine above S G 1 012, while the creatinine clearance is still approximately 60 ml /min , and the blood urea 40 mg per cent Even more [illegible]

venient function to study is the ability to concentrate which (if the quantity of urine is small) can be measured either by estimating the urine creatinine concentration or the urine osmolarity, or (if there is sufficient urine) simply by measuring the specific gravity The test is done at the end of a period of dehydration or, preferably, a few hours after the intramuscular injection of pitressin tannate in oil The advantage of studying the ability to concentrate instead of estimating clearances is that it avoids having to measure the rate of urine flow, a

mation, but there may also be similar shaped areas of ischæmic infarction; often the two are histologically inseparable. The extent of the vascular changes is very variable, but in those patients who have suffered from severe hypertension, advanced changes are always seen, both in the larger arteries and in the arterioles The arcuate, interlobar and interlobular arteries show gross thickening of focal areas of the external elastic lamina with fibrous replacement of varying amounts of the arterial walls, including the elastic and muscle coats; they may also show extensive fibrocellular proliferation of the intima These changes produce extreme narrowing of the lumen, though complete occlusion is rare The arterioles show the changes associated with either malignant or non-malignant hypertension

Whenever there are malignant hypertensive changes there are also widespread and severe changes in the larger arteries It is highly probable, therefore, that the presence of hypertension in chronic pyelonephritis is a sequel to partial occlusion of the larger arteries.

Clinical Features

In about 70 per cent. of all cases, chronic pyelonephritis is secondary to some persisting and continuing structural abnormality These have been described above in the section on acute pyelonephritis and are usually identified without great difficulty

The remaining patients with chronic pyelonephritis have developed their renal infection for no known reason and are usually very difficult to diagnose The following description concerns this second smaller group which consists mainly of children and women below the age of 40

The first indication that the disease is present may be.

1. Proteinuria in a "symptomless" patient
2. Hypertension and proteinuria in a "symptomless" patient
3. Advanced renal failure in a previously "symptomless" patient
4. A chronic intermittent illness with vague general symptoms and proteinuria
5. A recurrent illness with vague general symptoms but some localised signs, including loin pain, dysuria, fever and proteinuria

[illegible]

advanced, but also to the fact that even when there are symptoms [illegible] the patient and her attendant are apt to minimise their importance.

Frequency and dysuria occur in about half the cases but often

by an acute infection, an unexpected recovery may take place. For these reasons it is impossible to gauge the prognosis in an individual case until there is persistent and advanced renal failure, or malignant hypertension has developed. About half the patients with chronic pyelonephritis have a normal blood pressure, but it is nevertheless the renal disease which most frequently gives rise to malignant hypertension.

Sometimes, at autopsy, kidneys show widespread scars, similar to those found in chronic pyelonephritis but with no inflammatory cell infiltration; such lesions are known as "healed pyelonephritis." Their appearance frequently suggests that they have been present for a considerable time, yet they may be found in patients known to have

cause partial occlusion and hypertension some time after the cause of the scars has disappeared The prognostic implications are obvious; even if chronic pyelonephritis is successfully controlled, severe hypertension may develop at a later date

If chronic pyelonephritis is unilateral, total renal function remains within normal limits and the only danger is the development of hypertension

Unilateral chronic Pyelonephritis and Hypertension

It has been claimed that unilateral pyelonephritis is unlikely to be a cause of hypertension, for statistically the incidence of hypertension among patients with unilateral renal disease is the same as in the rest of the population Nevertheless, following the demonstration in animals that unilateral renal artery compression raises the blood pressure (p 77), many patients with unilateral renal disease and severe hypertension have had the diseased kidney removed in order to lower the blood pressure In about 20 per cent. of these cases the blood pressure has subsequently returned to normal and in most of the successful results the diseased kidney was infected or showed past evidence of infection

It is not yet possible to predict which patients, following nephrectomy, will have a fall in blood pressure Many of the successful operations have been in patients who had an acute and accelerated form of hypertension of short duration, including malignant hyper-

investigated by ureteric catheterisation

procedure fraught with many difficulties and inaccuracies when ureteric catheters The value of the technique is that it may no establish the diagnosis but, if the disease is essentially unilateral, gives an indication of the functional state of the less affected kid a factor of some importance if a nephrectomy is being contemp e.g. in order to lower the blood pressure.

Intravenous pyelography and retrograde pyelograms demons *inequalities* of structural damage and certain other characte changes One or more of the calyces may show a delay in emp the dye, and before the renal pelves become distorted there ma a persistent difference in their size. More definite changes later and include fixed distortions, flattening and gross reductio size of the renal pelves; often the ureters are dilated, though obstructed.

Retrograde pyelography and bilateral simultaneous renal fun tests both need ureteric catheterisation; it would seem reason therefore, to perform both tests consecutively on the same unfortunately, this is rarely successful and it is best to do then separate days.

Relationship Between Clinical and Structural Features

Renal biopsy studies have shown that there is a good correla between the structural lesions and the extent of functional impairm There is no relation, however, between the structural lesions and extent of the pyuria This is in keeping with the well-known clin observation that some patients may excrete considerable amounts pus each day for years without any marked deterioration of re function, whereas in other patients the increase in white cell excret may be slight and yet there is advanced renal failure.

Course and Prognosis

Pathologists claim that chronic pyelonephritis is the common cause of death from renal failure.

Occasionally the onset of the disease can be traced back to an acu upper urinary infection which occurred many years earlier, and whi was followed thereafter by intermittent mild relapses. More ofte the past is as indefinite as the future is uncertain.

It is characteristic of the progress of chronic pyelonephritis th renal functional impairment may either remain unchanged for 10–2 years, or suddenly become so much greater (due to an acute infectio that the patient dies within a few days. *It is equally characterist* that, though an almost terminal state of renal failure may be provoke

Once a diagnosis of chronic pyelonephritis has been made, the aim of treatment is to try and prevent the infection from smouldering or suddenly flaring up. Initially it is advisable to give a prolonged course of antibiotics. Thereafter, continuous and prolonged attention should be maintained by the patient and her doctor to detect any minor change in general condition, and the urine should be examined frequently If the patient experiences similar symptoms to those she has had with previous attacks or if there is fever, pains in the loins, dysuria or a sudden increase in white cell excretion, antibiotics should be started at once, whether or not the urine contains organisms If the patient is intelligent she can be given some tetracycline to keep at home and to take at the first sign of a recurrence Once a course of antibiotics has been started it should be continued for at least six weeks Sometimes recurrences are so frequent that it is best to give intermittent doses of antibiotics all the year round, either every few days, or a week's course once a month, very occasionally it is necessary to give antibiotics every day throughout the year The urine must be cultured at regular intervals during treatment to check on the sensitivity of the organism During pregnancy, a woman known to suffer from chronic pyelonephritis should be given prophylactic antibiotics throughout.

The choice of antibiotic depends on the sensitivity of the organism and the patient's reaction to its administration

Continuous or intermittent antibiotic therapy is sometimes attempted with only one drug, it is probable that a resistant strain is less likely to emerge, and side effects are less frequent if several antibiotics are used in rotation For instance, sulphadimidine 1 g 8-hourly, tetracycline 0 25 g 8-hourly, and Nitrofurantoin 0 1 g 8-hourly, can each be given for one week and the course repeated These doses are slightly smaller than those used for acute infections, they are usually sufficient and cause less side effects When there is renal failure toxic symptoms from overdosage can easily occur unless the dose is adjusted accordingly The most common disaster is to cause partial destruction of the vestibular nerve nuclei with streptomycin If the patient is acidotic, Mandelamine should not be used

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Chronic Urinary Infection and Renal Stones

There is no doubt that the presence of renal stones often causes urinary infections, but there is also some evidence that infection itself may cause stone formation The main factor which is probably responsible is the urea splitting properties of some organisms such as *B proteus*; ammonia is formed and the urine becomes, and remains, highly alkaline, which leads to the precipitation of calcium phosphate This mechanism is exacerbated if there is increased calcium excretion due either to excessive calcium intake (milk) or prolonged rest in bed (e g poliomyelitis).

Differential Diagnosis

Chronic bilateral pyelonephritis is most frequently confused with chronic glomerular nephritis and nephrosclerosis. In the absence of positive urine cultures, unilateral preponderance of structural and functional abnormalities, or characteristic radiological changes, the correct diagnosis can only be suspected from the appearance of the urinary deposit or the rate of cell excretion, the suggestive dissociation between the extent of tubular and glomerular functional impairment, and a renal biopsy In chronic glomerular nephritis the urinary deposit consists of large numbers of red cells and a few white cells, in chronic pyelonephritis there are large numbers of white cells and only a few red cells, whereas in nephrosclerosis there are only a few excess cells and these consist of about equal numbers of red and white. Renal biopsy may be useful in making the correct diagnosis.

Chronic pyelonephritis is the most common cause of unilateral renal disease

Treatment

If the disease is unilateral and the other kidney is sound it is usually wise to remove the diseased kidney, for, if the blood pressure is not raised preoperatively, the operation will prevent its rising; and, if it is already raised, the operation may cause it to return towards normal. Nevertheless, if the disease is not causing any symptoms, the urine is uninfected and the blood pressure is normal, it may occasionally be justifiable to do nothing except keep the patient under observation.

In bilateral disease any surgically treatable cause of urinary tract deformity, such as renal stone and ureteric strictures, should be attended to, but it is doubtful, once chronic pyelonephritis is established, whether surgical procedures will completely halt its progress. Postoperatively these patients should therefore be treated in the same way as those in whom no primary deformity of the urinary tract is discoverable, or in whom such a deformity is inoperable.

23

RENAL FUNCTION AND POLYURIA

THE functional disturbances which cause polyuria are (1) a lack of circulating antidiuretic hormone (ADH); (2) an inability of the tubules to respond to ADH, and (3) an osmotic diuresis (p 42). It is important to note that some of the clinical conditions which give rise to polyuria may be due to more than one of these disturbances This point is best demonstrated if the clinical causes of polyuria are listed under the three functional disturbances mentioned.

Polyuria Due to Lack of Circulating Antidiuretic Hormone (ADH)

(1) Diminished ability to secrete ADH because of disease of the supraopticohypophyseal system, i e diabetes insipidus.

(2) Diminished need to secrete ADH, because of continuous ingestion of water, i e compulsive polydipsia.

Polyuria Due to an Inability of the Tubules to Respond to ADH

(1) A congenital tubular defect, (*a*) as a single defect, i e. familial nephrogenic " diabetes insipidus " ; or (*b*) as one of several defects, i e Fanconi's syndrome

(2) An acquired tubular defect. (*a*) potassium deficiency; (*b*) high urinary excretion of calcium, (*c*) compulsive polydipsia; (*d*) chronic renal failure.

Polyuria Due to an Osmotic Diuresis

(1) Severe glycosuria, i e. diabetes.

(2) Chronic renal failure

Polyuria due to glycosuria is easily diagnosed by a routine test of the urine.

The other causes of polyuria can be subdivided into those that are associated with a moderate rise in blood urea and in which usually the urine volume is only increased to about 3–4 litres per 24 hours, and those that have a normal or low blood urea, and in which the urine volume is usually above 6 litres per 24 hours (often up to 10–12 litres).

Those conditions in which there is a rise in blood urea and only a moderate rise in urine volume include chronic renal failure, potassium deficiency, some cases of hypercalcuria, and the Fanconi syndrome,

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administration of water. Infants also greatly benefit from a low electrolyte diet, for this produces a quicker return to normal plasma osmolarity.

Diabetes Insipidus

It has been mentioned above that diabetes insipidus is due to a diminished ability of the supraopticohypophyseal system to secrete ADH This may follow a fracture of the skull, tumours, infections and lipoid storage diseases Not infrequently the cause is unknown It is more common in men than in women

The onset of symptoms is usually gradual and, once polyuria and polydipsia have developed, the daily water exchange remains relatively constant Sometimes 12-15 litres of fluid are ingested and excreted each day for many years, yet, in spite of the great disturbance to sleep, there may be no other symptoms or signs Loss of weight, exhaustion and constipation occur if the urine volumes become astronomical, i e 20–30 litres a day

Differential Diagnosis

The main difficulty in the differential diagnosis is to distinguish between diabetes insipidus and compulsive polydipsia Sometimes diabetes insipidus can be distinguished with relative certainty by finding other evidence of structural disease in the area of the neurohypophysis, or a diagnosis of compulsive polydipsia can be inferred from the patient's disturbed mental state and previous history of psychiatric peculiarities Often the distinction between these two conditions has to be made following the administration of pitressin and a period of dehydration, and on an estimate of the plasma osmolarity (See below)

Treatment

The administration of pitressin immediately relieves the thirst and polyuria The duration of this relief depends on the pitressin preparation and on the tubular capacity to concentrate The effect of pitressin tannate in oil, 5 units intramuscularly, should continue for 2–3 days, whereas the effect of pitressin snuff (25–50 mg) wears off after 3–6 hours

The disadvantage of pitressin tannate in oil is that the sites of injection are apt to feel a little sore for 2–3 weeks, while pitressin snuff is liable to cause sensitivity reactions such as rhinorrhœa and asthma, and the dosage is unreliable.

while those with a normal blood urea and the excretion of large volumes of urine include diabetes insipidus, compulsive polydipsia, some cases of hypercalcuria, and familial nephrogenic diabetes insipidus:

A *Polyuria with urine volume usually less than 3–4 l./24 hr. and blood urea raised*	B *Polyuria with urine volume often greater than 5 l./24 hr. and blood urea normal*
1 Chronic renal failure (p. 124)	[illegible]
2 Potassium deficiency (p. 150)	[illegible]
3 Hypercalcuria (p. 154)	[illegible]
4 Fanconi's syndrome (p. 160)	[illegible]

The disturbances included in Group A have been discussed in earlier sections. Those in Group B are discussed below, except for hypercalcuria, which has been discussed on p. 154.

CAUSES OF POLYURIA IN WHICH THE URINE VOLUME IS USUALLY GREATER THAN 5 l./24 HOURS AND THE BLOOD UREA IS NORMAL

Familial Nephrogenic Diabetes Insipidus

A rare sex-linked condition which occurs in males and with such a marked familial incidence that frequently there are several other cases under the same roof with the same symptoms. Occasionally chronic dehydration with plasma hypertonicity in infancy may lead to severe and permanent mental retardation. Investigation of entire families has shown that they may contain symptomless heterozygous female carriers, in whom there is a mild impairment of maximum concentrating capacity. The onset of symptoms is during infancy or childhood.

The disease is characterised by an almost complete inability to raise the urine concentration above the concentration of plasma with either 5 units of pitressin tannate in oil intramuscularly, or moderately severe fluid deprivation sufficient to cause a loss of up to 5 per cent. of body weight (Fig. 62), in both instances the urine usually remains around S.G. 1·004. If the pitressin dosage is raised to toxic levels (i.e. 2 units of the aqueous solution intravenously), or the dehydration is so severe that it gives rise to distress and fever, the urine concentration may then rise to much higher levels; this is sometimes seen terminally in nephrogenic diabetes insipidus of infancy.

Treatment consists mainly in early recognition and the adequate

assurance and encouragement are sufficient. Occasionally a rest in hospital will produce marked improvement and, if such a remission coincides with the administration of pitressin, an erroneous diagnosis of diabetes insipidus may be made. Usually stronger measures have to be employed, such as electro-convulsive therapy for the depression, and continuous narcosis for hysteria. Substantial remissions may be induced (Fig. 61) but the tendency to relapse is very great.

THE USE OF PITRESSIN AND DEHYDRATION TO DISTINGUISH BETWEEN DIABETES INSIPIDUS AND COMPULSIVE POLYDIPSIA

A distinction between compulsive polydipsia and diabetes insipidus can be made by (1) estimating and comparing the kidney's ability to concentrate the urine following the administration of pitressin and after a period of dehydration, (2) by observing the generalised effects of a long-lasting pitressin preparation, and (3) estimating the osmolarity of the plasma.

Estimate of the Kidney's Ability to Concentrate the Urine

Pitressin * is given to determine the efficiency of the kidney to concentrate the urine, and dehydration is used to test the ability of the neurohypophysis to secrete ADH. It is logical to do these tests in this order, for the presence of ADH following dehydration is inferred from the rise in the concentration of the urine, this, in turn, is dependent on the tubules' ability to respond to ADH.

Pitressin is given at a time when the patient's consumption of water is perfectly free and uninhibited, it is administered either intravenously as 100 m Units in 20 seconds followed by 5 m Units/min. thereafter for one hour, or intramuscularly as (1) pitressin tannate in oil, 5 units, or (2) aqueous pitressin 2.5 units. The test is most accurately performed with the first technique, but it is more convenient to use pitressin tannate in oil, for it is then unnecessary to catheterise the patient; nevertheless, pitressin tannate in oil may be dangerous for patients with compulsive polydipsia (p. 240).

Dehydration is a less precise test, for its ability to stimulate ADH production depends on the amount of fluid lost and not on the duration of dehydration. For instance, a period of 12 hours' dehydration is a stronger stimulus to ADH production in a polyuric patient unable to concentrate the urine, and who therefore excretes 3 to 5 litres of water, than is a 24 hour period of dehydration in a normal person who only

* Pitressin is the name given to the antidiuretic substance obtained from the neurohypophysis of animals after death, there is no evidence that it differs from antidiuretic hormone (ADH), the substance secreted by the neurohypophysis during life.

Compulsive Polydipsia

This is a much more common condition than diabetes insipidus. It is seen principally in middle-aged women. The onset of polydipsia and polyuria is often sudden and not infrequently it coincides with medical advice to drink more fluid (e.g. for constipation). The quantity of water which is consumed is apt to vary erratically from one day to the next, and frequently there is also a slow periodicity, with relapses and remissions varying from several weeks to months. Hysterical manifestations and depression are a part of the syndrome, and there is nearly always a long previous history of psychological disturbances; occasionally these patients are discovered to be magnifying the extent of their polyuria by pouring jugs of water into the bedpan.

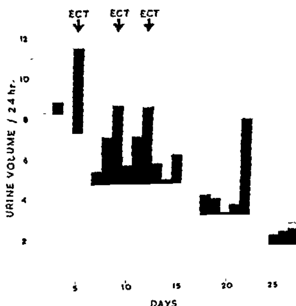


FIG 61 The effect of electro-convulsive therapy (ECT) on a patient with compulsive polydipsia and severe depression.

A diagnosis of compulsive polydipsia is usually suspected from the history and appearance of the patient, and often it is soon apparent that polydipsia and polyuria are the least of the patient's troubles. The differential diagnosis between diabetes and compulsive polydipsia is discussed below.

Treatment

The only treatment which is likely to succeed is one that controls the particular psychological disturbance involved. Sometimes re-

response to pitressin, though considerably greater than that following dehydration, is still below normal

Results of Pitressin and Dehydration Tests in Compulsive Polydipsia (Fig 62). These patients may respond in a variety of ways and the multiplicity of their responses is very confusing. The following responses are seen:

1 The kidney's ability to concentrate the urine following pitressin and dehydration is normal This response is only found in patients whose daily urine volume is around 4 to 6 litres

2 The kidney's ability to concentrate the urine following both pitressin and dehydration is impaired, but the concentration after dehydration is greater than after pitressin

This indicates that tubular function is impaired but the ability to produce ADH is normal In these patients the urine concentration with pitressin is about S G 1·010 and after dehydration S G 1·014

3 The kidney's ability to concentrate the urine following pitressin is normal, but following dehydration the urine remains hypotonic (i e the responses to the two tests is the same as in diabetes insipidus) This indicates that tubular function is normal, but there is an inhibition to ADH production which is not overcome by dehydration It may be difficult to differentiate such a patient from one suffering from diabetes insipidus, particularly if the aqueous or short-acting pitressin preparation has been used If pitressin tannate in oil has been given the distinction is usually easier (see below).

4 Finally, the kidneys are unable to concentrate the urine following pitressin, but the concentration after dehydration is even lower This indicates that there is a combination of tubular impairment and inability to secrete ADH The latter becomes more evident if pitressin is given during dehydration, for there is then a rise in urine concentration to a level well above that obtained with pitressin alone This response differentiates compulsive polydipsia from nephrogenic diabetes insipidus, where the tubular impairment is so severe that even the combination of pitressin and dehydration will not concentrate the urine above the concentration of plasma

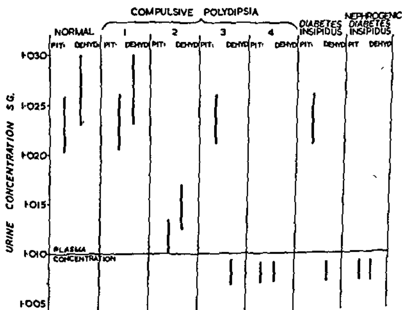
General Effects Following the Administration of a Long-acting Pitressin Preparation

If a patient suffering from compulsive polydipsia is given a long-acting pitressin preparation, i e pitressin tannate in oil, there is a considerable decrease in urine flow even if the tubules' capacity to concentrate is seriously impaired * (see above) But usually thirst

* Pitressin can lower the urine flow from 10 ml /min. to 2 to 3 ml without the concentration of the urine rising above S G 1 012, higher concentrations only occur at lower urine flows

loses 1·5 *litre* The most satisfactory method is to be guided by the weight that is lost *during dehydration, and to estimate the urine* concentration after the loss of 3 to 5 per cent of the initial weight. If greater losses are allowed the urine may become concentrated by mechanisms other than the neurohypophyseal secretion, and the test becomes pointless.

Theoretically the result of these two tests in diabetes insipidus and compulsive polydipsia should be as follows: patients with diabetes



FIG

insipidus should concentrate their urine normally with pitressin but not with dehydration, whereas patients with compulsive polydipsia

would be that of dehydration

Results of Pitressin and Dehydration Tests in Diabetes Insipidus (Fig. 62) Patients with diabetes insipidus are, indeed, unable to

per day for 10 days the ability to concentrate the urine following the administration of pitressin is seriously impaired (Fig. 63)

It is unknown why occasional patients suffering from diabetes insipidus respond poorly to pitressin These patients, in contradistinction to those with compulsive polydipsia, are probably dehydrated, so that according to the arguments advanced above they should concentrate rather more efficiently than normal persons In order to control their polyuria these patients require much larger quantities of pitressin

The patient's ability to secrete ADH is sometimes tested by other means than fluid deprivation For instance, the supraopticohypophyseal system can be stimulated by intravenous nicotine, or by suddenly raising the plasma osmolarity with an infusion of hypertonic saline Nicotine is only effective if it induces severe nausea and vomiting, while the results of infusing hypertonic saline are apt to be equivocal, for the salt causes an osmotic diuresis Neither of these two manœuvres gives as much information as a properly controlled period of fluid deprivation, which is in any case a more physiological stimulus for ADH secretion

Plasma Osmolarity

In compulsive polydypsia the osmolarity of the plasma is rarely above 280 m osmole/l, whereas in diabetes insipidus it is often greater than 290 m osmole/l

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"Acquired renal

F hritis A syndrome

continues unabated, and very quickly the intake of water exceeds the output, and acute overhydration develops. There is abdominal distension, headache, drowsiness, and eventually nausea and vomiting. In striking contrast, therefore, to patients suffering from diabetes insipidus, cases of compulsive polydipsia complain of the pitressin injections, often with much vehemence and bitterness. Occasionally, both the patient and his attendants are unaware that the onset of nausea, headache and drowsiness is related to the administration of

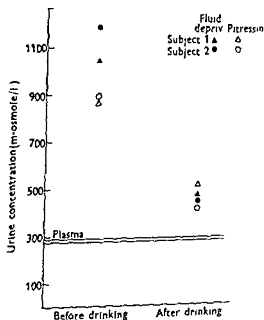


FIG. [illegible] administration of [illegible] ation, before and at [illegible] days The plasma [illegible] the two parallel [illegible] J Physiol)

pitressin Instead, these symptoms are considered to be additional evidence in favour of an intracranial lesion in the vicinity of the neurohypophysis, and therefore of a diagnosis of diabetes insipidus

Discussion

It is not at all clear why the kidney's ability to concentrate the urine following pitressin is sometimes impaired in compulsive polydipsia. Both the psychological disturbance itself and overhydration are possible factors, but the latter seems the more likely. This is supported by the fact that if normal subjects drink 8–12 litres of water

24

THE KIDNEY AND EMOTION

Emotion may cause either an antidiuresis or a diuresis. The *antidiuretic* response has been recognised for some time both in animals and in man It is identical with that obtained with pitressin and is

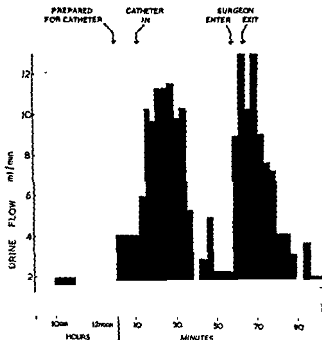


Fig 64 The effect on urine flow of (1) catheterising the bladder and (2) a brief interview with a surgeon The sudden increases in urine flow were due to osmotic diureses secondary to increased salt excretion The patient suffered from moderately severe hypertension (After Miles and de Wardener 1953, *Lancet*, 2, 539)

probably due to emotional stimulation of the supraopticohypophyseal system

An *emotional diuresis* is due either to an increased excretion of salt, when the increased urine flow is in the nature of an osmotic diuresis, or there may be an increase in urine flow without an increase

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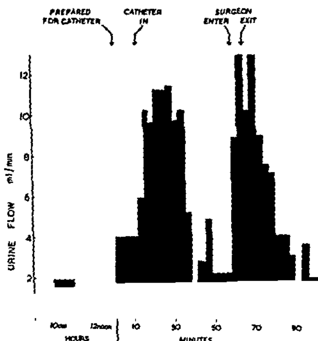


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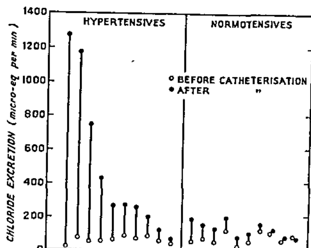


Fig 65 The effect on urinary chloride excretion of catheterising the bladder, in normal subjects, and in patients with hypertension; both groups were deprived of fluid for 24–36 hours before catheterisation (Miles and de Wardener, 1953, *Lancet*)

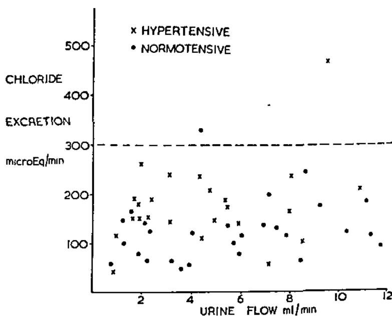


Fig. ... of water in normal

... by the increa...

in salt excretion, when the diuresis resembles that which follows the ingestion of water and is presumably due to a diminished secretion of antidiuretic hormone.

An emotional salt diuresis is due to a diminished tubular reabsorption of salt. It may take place in a few minutes (Fig 64) and its mechanism is quite obscure; adrenaline has been shown to have an opposite effect, and the sluggishness with which changes in renal function are produced by other suprarenal hormones make it unlikely that these are involved. A direct nervous effect on the tubules seems very likely

An emotional salt diuresis is most conspicuous in patients suffering from hypertension (Fig. 65) and has been the cause of much confusion During short-term experiments in these patients it has been frequently observed that the ingestion of water produces an increase in salt excretion proportional to the rise in urine flow, and it has therefore been concluded that the renal handling of salt in hypertension is abnormal It can be shown, however, that this is only an emotional artefact, for, if the observations are made without catheterising the bladder or performing venepunctures and in the absence of doctors, a diuresis provoked by a drink of water is not associated with an increased excretion of sodium chloride (Fig 66) In many hypertensive patients even the knowledge that an investigation has been planned is sufficient to provoke a salt diuresis, so that short-term observations are unsuitable for a study of their average metabolic state

It has also been shown that emotion can produce transient changes in glomerular filtration rate and renal blood flow

The clinical importance of these various emotional responses lie particularly in their ability to produce fictitious results when standard tests of renal function are being performed (p 38) The specific gravity of the urine following a period of dehydration may be no guide to the kidney's real powers of concentration, and similarly the response to a water load may be either exaggerated by a simultaneous salt diuresis, or completely inhibited When emotion causes a change in glomerular filtration rate, measurements of glomerular filtration will obviously be quite unrepresentative of the patient's normal state

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25

THE KIDNEY AND DISEASES OF THE CENTRAL NERVOUS SYSTEM

THE changes in renal function due to diseases of the neurohypophysis have been mentioned in Section 23 Alterations in renal function occurring in the course of other diseases of the brain are described below

A raised blood urea and proteinuria have frequently been observed in association with cerebral diseases, but often it is not clear whether these are related specifically to the accompanying central nervous lesion or to water deprivation. The curious tenet "never drip a head" is still prevalent in certain quarters and is occasionally responsible for extravagant and unnecessary deficiencies in both water and electrolytes When there is severe trauma to the central nervous system with hæmorrhage and hypotension, tubular necrosis and oliguria may occur, and are not particularly surprising Glycosuria frequently occurs, and may or may not be associated with hyperglycæmia; it is seen most often when there is hæmorrhage into the subarachnoid space

The most outstanding disturbances of renal function are those [illegible]

bulbar poliomyelitis, and lesions localised in the frontal lobe and hypothalamus The combination of increased salt excretion with hypochloræmia has been called " cerebral salt wasting " and has been studied more extensively than its reciprocal, for which no name has been coined, but which might be called " cerebral salt hoarding " In the salt-wasting condition large quantities of salt continue to be excreted despite low serum sodium and chloride and the patient may die of peripheral vascular failure Attempts to correct the blood levels are usually unsuccessful, for the salt excretion increases when salt is administered The defect does not appear to be due primarily to any change in the tubules, for they respond normally to ACTH. It is probable that it is due either to a disturbance of some part of the brain which controls the anterior pituitary, or the direct nervous connections between the brain and the kidneys.

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The most outstanding disturbances of renal function are those relating to salt excretion Both hyperchloræmia with hypochloruria and hypochloræmia with hyperchloruria have been reported They are associated with diffuse encephalitis, severe cerebrovascular disease, bulbar poliomyelitis, and lesions localised in the frontal lobe and hypothalamus. The combination of increased salt excretion with hypochloræmia has been called " cerebral salt wasting " and has been studied more extensively than its reciprocal, for which no name has been coined, but which might be called " cerebral salt hoarding " In the salt-wasting condition large quantities of salt continue to be excreted despite low serum sodium and chloride and the patient may die of peripheral vascular failure Attempts to correct the blood levels are usually unsuccessful, for the salt excretion increases when salt is administered The defect does not appear to be due primarily to any change in the tubules, for they respond normally to ACTH. It is probable that it is due either to a disturbance of some part of the brain which controls the anterior pituitary, or the direct nervous connections between the brain and the kidneys.

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widespread or focal, and the capillary lesions tend at first to involve only one part of a glomerulus.

The characteristic diabetic glomerular lesion consists of an accumulation of basement membrane-like material in a round mass at the periphery of one of the capillary loops, this substance stains pink with eosin (Fig 68). Such a collection tends to enlarge and obliterate the whole tuft; and as the disease progresses this becomes increasingly likely, for multiple lesions appear in each glomerulus The capillaries which give rise to excrescences of basement membrane material are dilated and appear to be partially obstructed These lesions, which are almost never seen in any other condition but diabetes, are sometimes referred to as "diabetic intercapillary glomerular sclerosis," or by the names of those who first described them, i e Kimmelstiel-Wilson

In addition to these specific vascular lesions the glomerula capillaries are usually diffusely thickened by infiltrating longitudin collections of collagen which are most dense near the origin of t glomerular arterioles These collections, which are stained pink w eosin, are the same as those found in many other renal disea including nephrosclerosis and the nephrotic stage of glomeru nephritis. They may, in their turn, obliterate the glomerulus without the typical Kimmelstiel-Wilson lesion being present

Both these glomerular lesions are usually found in association with gross thickening of the afferent and efferent arterioles (mainly the afferent) of the glomeruli involved The arteriolar walls keep their sharp outline (unlike the appearances in fibrinoid necrosis), but are widened by some material which stains a deep and vivid pink with hæmatoxylin and eosin, the composition of this substance is not known; it is not collagen or basement membrane-like material

The tubules show similar changes to those found in the nephrotic stage of glomerular nephritis, and very occasionally the proximal tubules contain large quantities of glycogen The interstitial tissues contain varying collections of chronic inflammatory cells, in proportion to the number of glomeruli which are disintegrating

Finally, the changes of hypertension and chronic or acute pyelonephritis are frequently found superimposed upon those just described

Clinical Features

The first sign is always proteinuria, and in the young this may become sufficiently massive to give rise to a typical nephrotic syndrome Patients over 50 years of age are more likely to present with chronic renal failure and hypertension Whichever course is taken, the average

Diabetic Nephropathy

Widespread vascular abnormalities occur frequently in long-standing diabetes. They differ from the common forms of hypertension or atheromatous vascular changes and are situated in the retinal veins

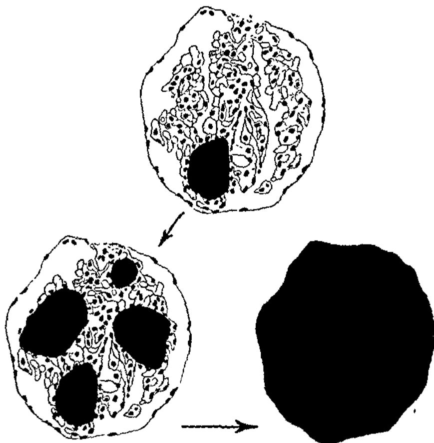


FIG 68 Diabetes (Kimmelstiel-Wilson lesions). Schema illustrating the peripheral distribution in the glomerulus of the characteristic deposits of eosin staining material, and how eventually they may entirely fill the glomerulus The non-specific lesions which also occur in diabetic nephropathy (see text) are not shown

and arteries, the arteries to the peripheral nerves, and the renal arteries and capillaries The renal lesions can cause death.

Pathology

The kidney may be of normal size or even a little larger than normal. The vascular lesions involve the glomerular capillaries and both the afferent and efferent arterioles. Their distribution may be

widespread or focal, and the capillary lesions tend at first to involve only one part of a glomerulus.

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through both ureters, whereas with the second, protein is present only on the left side. In order, therefore, to distinguish orthostatic from other causes of proteinuria, the urine should be tested for protein, *after* the patient has been lying on her side.

Ureteric and Pelvic Dilatation

After the third month of pregnancy the ureters and *renal pelves* are usually dilated. Initially this is due to a *ureteric and pelvic* atony, possibly caused by hormonal changes accompanying pregnancy. Paradoxically the atony is associated with hyperplasia of the ureteric muscles; there is also an increase in the connective tissue within the ureteric walls. *Later, as the uterus enlarges, it compresses the ureters* at the pelvic brim, this mechanical obstruction is superimposed upon ureteric atony and the combination results in considerable ureteric dilatation. Normally the uterus is tilted towards the right side and, in consequence, it is usual to find the ureteric dilatation on the right to be greater than on the left.

These changes are more marked in primigravidæ than in multiparæ.

RENAL INFECTIONS

Acute pyelonephritis * is the most common *complication of* pregnancy, it occurs in about 1 per cent. of all pregnancies. The dilatation, atony and compression of the ureters (see above) produce a partial obstruction to the flow of urine which appears to favour the incidence of infection. The way the infection reaches the kidney is unknown, but it is probable that the organisms ascend *from below*. *It* has been established that the urine of about 10 per cent. of all normal symptomless pregnant women contains organisms, and these have almost certainly entered the bladder through the urethra.

Acute renal infections also occur quite frequently after delivery. For the first few days of the puerperium, about 15 per cent. of women have some difficulty in initiating micturition because of episiotomies, prolonged labour, etc., they are apt to get overdistended bladders and have residual urine after voiding. About 40–50 per cent. of these patients develop an acute urinary infection.

Clinical Features

The incidence of acute pyelonephritis begins at the fourth month;

[illegible] renal infection in pregnancy an acute [illegible]ly severe infections [illegible]o a *staphylococcal* [illegible]onformity with the

the infection is either bilateral or, when unilateral, it is usually on the right side.

The physical signs and symptoms have been described on p. 219. Mild cases only complain of backache; they may admit to occasional feverish symptoms or pain on passing water with some reluctance, considering that such symptoms are normal in pregnancy. Some attacks may be associated with such severe vomiting that the patient is thought to be suffering from hyperemesis gravidarum.

As in all forms of renal infection the most helpful diagnostic features are rigors, tenderness in the costo-vertebral angles, the presence of white cells and organisms on microscopical examination of the urine, and a positive urine culture. As a sign of renal inflammation, however, the value of a positive urine culture is diminished by the fact that so many pregnant women have organisms in their urine without any evidence of renal inflammation or cystitis; the presence of white cells in the urine is therefore more important. (From a therapeutic point of view the distinction disappears, for organisms should not be allowed to remain in any part of the urinary tract.)

An intravenous pyelogram should only be performed if there is reason to believe that there is a calculus, an ectopic kidney, or there are recurrent infections difficult to control. The number of films should be strictly limited for recent statistical evidence suggests that acute leukæmia in children may follow fœtal exposure to diagnostic X-rays. A unilateral *left-sided* infection is particularly likely to be due to some additional disturbance of the renal tract, such as a calculus.

Treatment

The treatment of acute pyelonephritis has been discussed on p. 221. The liability to relapse is particularly great in pregnancy, and treatment with antibiotics should be continued for at least a month. If nevertheless there is a second attack, and evidence of renal (as opposed to bladder) infection is unequivocal, treatment should continue until the end of pregnancy.

Prognosis

Before the introduction of antibiotics about one-third of women who had had acute pyelonephritis during pregnancy developed chronic pyelonephritis subsequently. Since that time there has been a great improvement in treatment and the prognosis is brighter. After delivery, however, all cases should be carefully followed up, repeated samples of urine should be cultured, and if infection continues an intravenous pyelogram should be performed. Even the presence of bacteria in the urine, without an increase in the number of white cells (i.e. bacilluria), should be treated promptly and energetically.

epigastric pain, sometimes of great severity. From the initial symptom to the first convulsion the syndrome may be telescoped into a matter of hours; fortunately the development of symptoms is usually slower. There is always some degree of oliguria. With the convulsions there may be temporary anuria, and very occasionally acute renal failure develops. Unless there is acute renal failure the specific gravity of the urine during a period of oliguria is high.

After delivery the symptoms and signs usually subside rapidly, though in exceptional cases the most prominent features of the disease may occur in the first two to three days of the puerperium.

Differential Diagnosis

It is essential to exclude contamination of the urine by vaginal discharge, and confirmation of the presence of "renal" proteinuria should be obtained by catheter specimens of urine

If persistent proteinuria is found before the twentieth week it is most unlikely to be due to toxæmia of pregnancy. At this time the most common causes of proteinuria are orthostatic proteinuria and chronic renal disease Excluding acute pyelonephritis, which is not difficult to diagnose, other acute renal diseases are very rare during pregnancy (p. 268). Other causes of proteinuria include cardiac failure, severe anæmia and renal tuberculosis

If the urine is not examined before the twentieth week, and proteinuria is found subsequently, *all these causes of proteinuria must be considered* as well as the probability of toxæmia of pregnancy.

Prognosis

The immediate prognosis of toxæmia of pregnancy is excellent, unless there are fits; the mortality of eclampsia varies between 10–40 per cent, one of the causes of death being acute renal failure.

The ultimate prognosis is difficult to assess. Following toxæmia of

that the incidence of hypertensive vascular disease in women is the same *whether or not they have* borne children. The conclusion, which is generally accepted, is that persistent hypertension following toxæmia of pregnancy only develops in women who were inevitably bound to

toxæmia of pregnancy

following toxæmia of pregnancy varies considerably in different series. *A recent report*

tates that it is 20 per cent following eclampsia and 40 per cent ollowing non-convulsive toxæmia This paradox was attributed to (1) the fact that non-convulsive toxæmia usually lasts longer than eclampsia, for there is a positive correlation between the duration of toxæmia and residual hypertension, and (2) the diagnosis of non-convulsive toxæmia is often uncertain and may include some patients who had hypertension before pregnancy who may, therefore, only have essential hypertension

There is no evidence that toxæmia of pregnancy gives rise to chronic renal disease other than that which may accompany hypertension.

When a woman has had non-convulsive toxæmia of pregnancy in her first pregnancy the incidence of toxæmia in the second pregnancy is about 30 per cent If a multiparous woman has had non-convulsive toxæmia the incidence of a recurrence of toxæmia with a subsequent pregnancy is about 60 per cent These figures are slightly less following eclampsia, and greater in women with persistent hypertension between pregnancies

Treatment

Toxæmia of pregnancy is unlikely to occur in women who avoid putting on more than 5 lb in any one month or more than 10 lb in the last three months If these limits are exceeded a low-salt, high-protein, low-calorie diet is given with vitamin and mineral supplements until the position has been readjusted

Once toxæmia of pregnancy has declared itself the best treatment is bed rest, sedatives and a similar diet to that described above, except that it should be as salt-free as possible If the blood pressure continues to rise, with increasing proteinuria and the development of retinal changes, hypotensive drugs or spinal anæsthesia can be tried while the effect of the salt restriction and bed rest are given time to take effect, if there is a continued and uncontrollable deterioration, pregnancy must be terminated The treatment of hypertensive encephalopathy consists in sedation, lowering the blood pressure, and termination of pregnancy

It is important to keep in mind that acute renal failure may develop, in order that its treatment may not be delayed

ACUTE RENAL FAILURE DURING PREGNANCY

Acute tubular necrosis is the commonest cause of acute renal failure in pregnancy It may follow eclampsia, or severe pre-eclamptic toxæmia, accidental hæmorrhage and post-partum hæmorrhage It occurs most commonly, and is most severe, with accidental hæmorrhage

at about the sixth to seventh month of pregnancy; it is exceedingly uncommon following post-partum hæmorrhage.

The cause of the necrosis is an acute renal ischæmia which, in the case of accidental and post-partum hæmorrhage, is due in part to a reduced blood volume. It is possible that there may be in addition a direct nervous vasoconstricting stimulus from the uterus to the kidneys (p. 60).

Occasionally eclampsia may cause acute renal failure because of widespread arteriolonecrotic lesions, similar in all respects to those found in malignant hypertension

Pathology

The ischæmic tubular necrosis may be focal as described on p. 110, or may be so extensive that the entire cortex is involved, when the condition is known as "cortical necrosis." In the more severe and extensive lesions the arteries are also necrosed and contain thrombi.

Clinical Features, Course and Treatment

The diagnosis of acute renal failure is often delayed because of the more immediate threat to life from accidental or post-partum hæmorrhage. The clinical features and treatment of acute tubular necrosis have been described on p. 115.

One of the aims of treatment is to prevent the development of acute renal failure In eclampsia the use of hypotensive drugs or caudal anæsthesia to produce a widespread vasodilatation will not only lower the blood pressure and control the convulsions, but will diminish the renal vasoconstriction and prevent tubular necrosis.

Often with accidental hæmorrhage, the quantity of blood that has been lost is underestimated; a continuous slow hæmorrhage from afibrinogınæmia is not recognised; and there is a paralysing fear of transfusions because the patient has oliguria. These three factors, in combination, greatly favour the development of acute tubular necrosis. It is essential that the lost blood should be replaced quickly and adequately and that transfusions should continue until bleeding has ceased. In this way renal vasoconstriction diminishes and tubular necrosis may be avoided.

PREGNANCY IN RELATION TO PRE-EXISTING CHRONIC RENAL DISEASE

Opinions vary. Addis, after a long experience in California, stated that " There is no instance in which we can be sure that the renal lesion

interfered with pregnancy. There is no evidence that any of them have been harmed by pregnancy." Other authors are less sanguine The opinions given below are those most widely held; there is little quantitative information available.

The Effect of Chronic Renal Disease on Pregnancy

The outstanding fact is that women with chronic renal disease (particularly glomerular nephritis) are usually sterile Those who do become pregnant are extremely liable to abort at the third to the fifth month of pregnancy, or to develop accidental hæmorrhage later Toxæmia of pregnancy and eclampsia are uncommon complications Some women have a normal pregnancy, though the fœtus is apt to be small It is probable that the prognosis depends on the height of the blood pressure before conception, as well as the extent of the renal failure

Because of the dangers of accidental hæmorrhage it is usual to terminate pregnancy, if the fœtus is sufficiently large, at about the thirty-third week

The Effect of Pregnancy on Chronic Renal Disease

With glomerular nephritis the issue is relatively clear cut Either there is a sudden deterioration in renal function, with increased proteinuria and a rise in blood pressure before the twentieth week, or pregnancy causes no harm When there has been an exacerbation of the renal disease some permanent additional impairment of function remains thereafter

With other renal diseases, such as chronic pyelonephritis or polycystic disease, the prognosis depends more directly and less mysteriously on whether or not renal infections are allowed to develop.

It is nearly always impossible to predict the probable course of events If a woman with chronic renal disease is anxious to have a

begun renal infections should be prevented (see p 231), and renal function, urine deposit, the extent of the proteinuria and the height of the blood pressure carefully watched Pregnancy is discontinued at once if there is evidence of an exacerbation of renal disease.

Women with chronic renal disease and hypertension and/or moderately well advanced renal failure should not become pregnant, for any further deterioration in renal function may be crippling Pregnancies should be terminated if they occur.

Unilateral Kidney

When there is only one kidney pregnancy should not be attempted until the functional and structural state of the kidney has been examined; it should be remembered that a nephrectomy is often performed for a renal disease which may be bilateral.

THE INCIDENCE OF OTHER RENAL DISEASES IN PREGNANCY

Excluding renal infections, the onset of a new renal disease during pregnancy is very rare Acute glomerular nephritis is the most common There is no difficulty in diagnosis if attention is paid to the jugular venous pressure and the urinary deposit. The sudden onset of heart failure and rise in blood pressure excludes other causes of proteinuria and oedema. If the acute phase of the disease is safely negotiated pregnancy may continue normally with no permanent deterioration of renal function evident.

Very occasionally nephrotic glomerular nephritis may develop for the first time during pregnancy The massive proteinuria, the normal blood pressure and jugular venous pressure distinguish the diagnosis. Such patients have occasionally been successfully treated with cortisone or prednisone and had a normal pregnancy.

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29

RENAL DISTURBANCES ASSOCIATED WITH FUNCTIONAL DISORDERS OF THE SUPRARENAL GLAND

Adrenal Medulla

Phæochromocytoma

THESE tumours may cause a fluctuating or, more commonly, a persistent hypertension, the latter is often malignant. Renal functional and structural changes are those found with hypertension from any cause (p. 82). Except with malignant hypertension, it is unusual for there to be any serious impairment of renal function.

When renal function is normal, adrenaline blocking agents such as phentolamine (Rogitine) cause a fall in blood pressure which is presumptive evidence that the pre-existing increase in blood pressure was due to an excess of circulating adrenaline and nor-adrenaline. It must be remembered, however, that phentolamine may also cause the blood pressure to fall when it has been raised by renal disease (p 138)

Adrenal Cortex

Primary Aldosteronism

This syndrome was first described in 1955. It has already been discussed on p. 153.

The outstanding function of aldosterone is to decrease sodium, and increase potassium excretion in the urine. The features of aldosteronism, however, are almost entirely confined to its effect on increasing potassium excretion; presumably its sodium retaining properties are compensated for by other mechanisms which control sodium metabolism There is a continuous leak of potassium in the urine, and an increasingly negative potassium balance This results in a characteristic vacuolation in the cells of the tubules, particularly in the proximal tubules; and there is a simultaneous impairment of many distal tubular functions The ability to concentrate the urine gradually diminishes until a concentration above that of plasma is no longer possible, but the ability to dilute remains, and large quantities of hypotonic urine are passed. The ability to excrete an acid urine is

severely impaired, but the production of urinary ammonia is only affected to a small extent.

Glomerular function is disturbed later than tubular function, and not so seriously; proteinuria is usually present from the beginning.

The clinical features are those of (1) potassium deficiency including periodic attacks of generalised paralysis (p. 151), E.C.G. changes, hypochloræmia with alkalosis, and polyuria and polydipsia; (2) hypertension in most cases, and (3) in a few instances an increased concentration of sodium in the plasma; oedema is unusual.

The differential diagnosis is discussed on p. 152.

Hyperadrenalism (Cushing's Syndrome)

In this condition there is an increased urinary excretion of 17-ketosteroids and ketogenic steroids In large quantities these hormones have the same properties as aldosterone, and thus Cushing's syndrome is often associated with excess potassium excretion, negative potassium balance and alkalosis. These changes are rarely as severe as in aldosteronism. In addition, patients with Cushing's syndrome are apt to suffer from depressed osteoblastic activity → osteoporosis → hypercalcuria → renal stones These may give rise to renal infection, hydronephrosis, etc.

Adrenal Insufficiency

The renal disturbances associated with adrenal insufficiency are:

1 Depressed glomerular filtration rate.
2 Increased urinary excretion of sodium, which with the onset of acute deficiency results in negative sodium balance and a contraction of the extracellular fluid volume
3 Decreased urinary excretion of potassium resulting in a raised plasma potassium concentration.
4. Diminished ability to excrete a water load.
5 Diminished ability to excrete a sodium load
6 Absence or reversal of the diurnal rhythm.

The depressed *glomerular filtration rate* is due in part to the contraction of the extracellular fluid volume, but also to the absence of the normal direct effect on the renal vasculature of those adrenal steroids which are concerned with the maintenance of a normal renal blood flow Regardless of changes in the extracellular fluid volume therefore the renal blood flow in adrenal insufficiency is lower than normal. The *blood urea* tends to be raised; this not only follows directly from the fall in glomerular filtration rate, but also from an increased protein breakdown which sometimes accompanies adrenal insufficiency, particularly when its onset is acute.

The *sodium* leak and *potassium* retention, the impaired ability to excrete a *water* or *sodium load* and the abnormality in the *diurnal* rhythm all result from disturbances in tubular function. Other impairments in tubular function can sometimes be demonstrated, such as a diminished ability *to excrete an acid urine* and a reduced capacity to *excrete ammonia*; the ability to *concentrate the urine* is also moderately depressed These abnormalities appear to stem directly from the

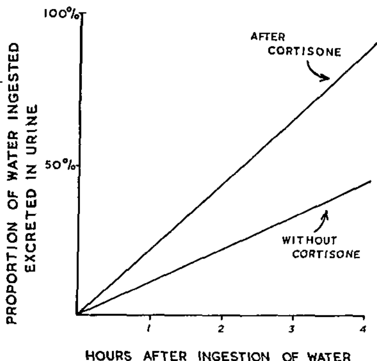


FIG 70 The effect of cortisone on the impaired ability to excrete a water load, in a patient with Addison's disease

diminished concentration of steroids in the blood supplying the tubules

Water Tests for Adrenal Insufficiency. The diminished ability to excrete a water load is an important part of the Robinson Power Kepler test for the diagnosis of adrenal insufficiency, for the first part of this test is concerned entirely with water excretion Food and fluids are withheld from the patient from 6 p m At 10 p m the patient is asked to empty his bladder and this urine is discarded All urine is now collected and the volume passed between 10 p m. and 7 a m is collected together and measured as one sample At 7 a m, immediately after

the bladder has been emptied, 850 ml. of water per sq m. is given in half an hour (for a man of average weight this is about 1,500 ml.) The urine is collected thereafter at 8, 9, 10 and 11 a m In normals, the volume of urine passed during one of these hourly periods exceeds the 10 p.m to 7 a m. volume, whereas in adrenal insufficiency none of the hourly samples exceeds the overnight volume The test is positive in about 90 per cent. of patients with adrenal insufficiency, but a few patients with other conditions, such as ulcerative colitis, ileal insufficiency and rheumatoid arthritis may also give abnormal responses.

The ability to excrete a water load rapidly, returns to normal following the administration of cortisone. This sudden reversal forms the basis of another test for adrenal insufficiency. A litre of water is given in the morning and the urine is collected at hourly intervals thereafter, for four hours The test is repeated on the next day, beginning an hour after the administration of 100 mg cortisone If the patient suffers from Addison's disease the amount of water he will excrete in the four hours without cortisone will be less than 800 ml. but on the next day it will be nearer 1,000 ml (Fig. 70) Unfortunately a similar decrease in the ability to excrete a water load which can be improved by cortisone has also been reported in patients with chronic liver disease and small bowel insufficiency

Adrenal Insufficiency Superimposed upon Pre-existing Structural Renal Disease. This combination of circumstances is encountered when bilateral adrenalectomy is performed upon a patient suffering from malignant hypertension

Treatment of the adrenal insufficiency can be very difficult Either not enough cortisone is given, the glomerular filtration falls and the blood urea rises rapidly, or too much is given, when the catabolic effect of cortisone is apt to release large amounts of potassium into the plasma On account of the renal disease there is little or no compensatory increase in potassium excretion, and a dangerous rise in the plasma potassium concentration may occur

It is essential that both these eventualities be kept in mind The excretion of potassium is maximal only if a sufficient quantity of salt is given A rapid rise in plasma potassium may be controlled by the administration of testosterone, which diminishes the catabolic effect of cortisone Occasionally it may be necessary to interrupt the administration of cortisone, and substitute desoxycorticosterone.

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30

RENAL VEIN THROMBOSIS

THROMBOSIS of the renal veins is an extremely rare condition. The thrombus may either originate in the inferior vena cava and spread laterally into the renal veins, or it may begin in the smaller veins within the parenchyma of a diseased kidney and spread medially.

Pathology

The usual biopsy specimen, obtained several weeks or months after the onset of the thrombosis, usually shows merely a few insignificant and unspecific changes, and is only of value in a negative sense. One renal biopsy, performed a few days after the onset, showed extensive interstitial oedema.

At autopsy the diagnostic feature is the finding of a thrombus in the renal vein with, in long-standing cases, the presence of large collateral venous channels between the capsule of the kidney and the surrounding tissues. Microscopically the glomeruli appear normal and the tubules are unchanged unless there has been much proteinuria, when the tubule cells will contain lipoid material and collections of an eosin staining substance, though in some long-standing cases there is considerable tubular atrophy and tubular separation.

Inferior vena caval thrombosis may be spontaneous, or may be due to invasion by neoplasm, or to external compression. The most common renal disease to give rise to intrarenal venous thrombosis in adults is renal amyloidosis; it occasionally occurs with chronic pyelonephritis. In infants renal vein thrombosis is often associated with acute pyelonephritis.

Clinical Features

These depend on the rapidity of the thrombotic process, whether it is unilateral or bilateral, and if it is secondary to inferior vena caval thrombosis.

When the thrombosis is rapid, bilateral, and has spread from the inferior vena cava, there is sudden oliguria, proteinuria, and renal failure with oedema of the lower limbs and the anterior abdominal wall. Death may occur rapidly from acute renal failure.

If the thrombosis is bilateral but the inferior vena cava is unobstructed there is no oedema of the lower limbs. In adults this is usually

due to renal disease. In infants acute bilateral renal vein thrombosis often follows acute gastro-enteritis, when the thrombosis is presumably caused by intense renal ischæmia in otherwise normal kidneys; or it may be associated with acute pyelonephritis ; there is usually sepsis elsewhere, and the sudden onset of flank tenderness and pyuria with a swinging fever may suggest the diagnosis. Acute renal failure and death are the usual outcome.

Occasionally, however, the onset of bilateral renal vein thrombosis in adults (whether or not it is associated with inferior vena caval thrombosis) is less acute and may pass unnoticed, or the initial disturbance is followed by a large measure of recovery. Some of these cases may subsequently develop a nephrotic syndrome and, unless it is accompanied by evidence of inferior vena caval thrombosis with large collateral channels on the anterior abdominal wall, the thrombosis of the renal veins is unsuspected. In a few patients all evidence of renal disturbance may disappear except for the continued presence of a mild proteinuria

The clinical course probably depends on the ability to recanalise the thrombus and establish a collateral venous circulation

Diagnosis

The sudden onset of oliguria, proteinuria, raised blood urea, and severe oedema confined to the lower limbs, without evidence of cardiac failure or hypoproteinæmia, should make one suspect the condition Collateral venous channels on the anterior abdominal wall do not appear until several weeks or months after the onset, but once they are evident they greatly simplify the diagnosis in those cases of inferior vena caval and renal vein thrombosis who have survived the acute phase.

Renal vein thrombosis without inferior vena caval thrombosis is the most difficult variant to diagnose. Renal vein obstruction can sometimes be demonstrated by rapidly injecting about 50 ml of a 70 per cent. solution of diodone into the inferior vena cava This is given through a catheter which is introduced into the inferior vena cava via the saphenous or the antecubital vein In order to force the diodone solution upstream into the renal veins, the intrathoracic pressure is suddenly raised at the start of the injection This can either be done voluntarily by the patient performing a Valsalva manœuvre, or, if a preliminary trial shows that he finds it difficult to do this adequately, he is anæsthetised and the intrathoracic pressure is raised by pressure on the anæsthetic bag. This procedure is only useful if the thrombosis is present in the principal branches of the renal vein ; it does not reveal thromboses confined to the interlobar veins.

Treatment

If the onset is recognised in adults it is reasonable to give anticoagulants; otherwise treatment is symptomatic

In infants with pyelonephritis a nephrectomy may prevent the spread of the septic thrombus into the inferior vena cava and across to the other kidney.

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31

RENAL ARTERY THROMBOSIS

An uncommon condition which occurs particularly in elderly patients with advanced atheromatous vascular disease who have previously suffered from cerebral or coronary thrombosis, or peripheral arterial disease

Pathology

The thrombus is either in the main renal artery or it may be confined to one or two of its branches. With occlusion of the main vessel the kidney becomes smaller, pale and bloodless If, however, some of the renal veins become thrombosed at the same time there will be localised areas of congestive and interstitial oedema.

Clinical Features

In contrast to renal vein thrombosis the outstanding presenting symptom is severe pain. The patient usually presents as an acute emergency, either abdominal if the pain is in the flank or hypochondrium, or cardiac or respiratory if it radiates to the lower chest. Nausea and vomiting are common

There is acute tenderness in the renal angle and flank, but there may be no rigidity. Hæmaturia sometimes occurs, presumably if there is a concomitant thrombosis of the renal veins.

A straight X-ray of the abdomen often shows a calcified abdominal aorta and an I V P confirms that the condition is renal, for no dye is secreted on the side of the pain and tenderness. At cystoscopy no urine is seen emerging from the ureteric orifice, but a retrograde pyelogram shows a normal pelvis and calyces. Subsequently the affected kidney becomes smaller while the normal kidney becomes larger. An aortogram confirms that there is no blood flow into the renal artery of the affected kidney.

Prognosis

The immediate prognosis is more concerned with the functional integrity of the other organs, e g. whether cardiac failure was present before the renal arterial thrombosis occurred.

Occasionally when the patient survives there is a sudden onset of severe malignant hypertension in the next few weeks.

Treatment

The patient's general condition usually precludes any measures other than those of anticoagulant therapy, rest and symptomatic treatment.

If the thrombosis occurs in a young subject, because of a localised structural anomaly of the renal artery, the kidney should be removed, particularly if the blood pressure begins to rise.

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32

HÆMOGLOBINURIA

Hæmoglobinuria is the term used for the appearance of free hæmoglobin in the urine. It follows hæmolysis of red cells, either in the blood stream or in the urine

Free hæmoglobin is about the biggest naturally occurring molecule that can pass freely through the normal glomerular membrane (mol wt 68,000). At low plasma concentrations all the hæmoglobin that is filtered is reabsorbed, it does not appear in the urine until the plasma

molecule is converted into hæmosiderin and excreted into the urine Hæmosiderinuria will therefore be present when there is free hæmoglobin in the plasma whether or not there is hæmoglobinuria.

Myohæmoglobinuria occurs when there has been considerable injury to muscle (e g crushing accidents). Myohæmoglobin is a muscle protein with a molecular weight of 17,000; it permeates freely through the glomerulus, and little seems to be reabsorbed by the tubule; it first appears in the urine when the plasma concentration is about 10 mg. per cent, and its rate of excretion is extremely rapid For this reason it is rarely detected in the blood

Methods of Identification

Hæmoglobin and Myohæmoglobin

These can be identified in solution, either spectroscopically or by the colour that is produced when they react with tolidine. A few milligrammes of purified tolidine hydrochloride are dissolved in 5 ml of glacial acetic acid; 1 ml. of this solution and 1 ml. of freshly prepared hydrogen peroxide are added to 2 ml of urine The presence of hæmoglobin or myohæmoglobin in considerable amounts will turn the urine blue, a lesser amount will only produce a green colour.

Hæmosiderin

In contrast to hæmoglobin and myohæmoglobin which are in solution, hæmosiderin in the urine is present in particulate form, either in disintegrating tubule cells or as amorphous debris. The test for

hæmosiderinuria consists, therefore, in using the Prussian blue reaction to stain the urine sediment. About 20 ml of urine is centrifuged and all but 1 ml of the supernatant fluid is discarded 1 ml. of 5 per cent. hydrochloric acid and 0.5 ml of a 10 per cent. aqueous solution of potassium ferrocyanide are then added to the 1 ml of urine in which the deposit has been resuspended A drop is then examined under the microscope, when hæmosiderin will appear as deep blue flecks lying free or within the tubule cells and casts.

Renal Changes Associated with Hæmoglobinuria

Acute Changes

Large amounts of hæmoglobin have been given experimentally both to normal man and animals. There are either no adverse renal effects, or only a transient reduction in renal blood flow and glomerular filtration rate

Under clinical conditions, however, hæmoglobinuria is occasionally associated with acute renal failure It has also been observed that if hæmoglobin is given to animals that are oligæmic or dehydrated, tubular necrosis may occur with numerous hæmcasts in the distal and collecting tubules.

It is probable, therefore, that several closely connected factors are responsible for the renal failure that follows clinical hæmoglobinuria Pre-existing oligæmia or dehydration are usually present, and have caused renal vasoconstriction before the onset of hæmoglobinuria, and have also resulted in a high concentration of circulating anti-diuretic hormone (ADH). Hæmoglobinuria then accentuates the vaso-constriction, and the resulting renal ischæmia causes focal necrosis and a gross reduction in glomerular filtration rate Finally the raised ADH concentration and the reduced filtration rate result in a maximal reabsorption of water from the filtrate, this favours the formation of hæmcasts, which in turn may possibly obstruct the nephrons in which they are situated

The pathological changes have been described in Section 12 There are focal areas of tubular necrosis, hæmcasts and occasional collections of interstitial inflammatory cells Large amounts of hæmosiderin may be found in the tubule cells

Chronic Changes

There are two functional changes, proteinuria and a reduction in the renal threshold for hæmoglobin Whereas normally hæmoglobinuria only occurs at plasma concentrations greater than 100 mg /100 ml, following several hæmoglobinuric crises, hæmoglobin

The disease becomes manifest usually between the ages of 20 and 40, and occurs equally in both sexes The tendency to hæmolyse fluctuates, and during relapses hæmoglobinæmia is continuous, though hæmoglobinuria comes on in sudden sharp attacks In addition to the discoloured urine these acute episodes are associated with headache, backache, muscular and abdominal pains. Acute hæmolytic crises are sometimes brought on by mild infections. There may be severe anæmia and there is a continuous reticulocytosis; eventually the patient develops a pale brown pigmentation. Occasionally there may be remissions of a few weeks or months when the total blood hæmoglobin concentration returns to normal, but hæmosiderinuria continues uninterruptedly. Death usually occurs from thrombosis of visceral veins including the mesenteric, splenic and renal

The anæmia cannot be treated with transfusions of ordinary blood, for these cause an intense hæmolysis of the *patient's* red cells This reaction is due to some substance present in the donated plasma, and can be avoided by giving red cells washed and suspended in saline

Blackwater Fever

This complication of malignant tertian malaria usually occurs in those who have previously been treated with antimalarial drugs, particularly quinine, either prophylactically or for recurrent attacks of malaria There is a sudden and severe hæmolysis of unknown cause, sometimes followed by acute renal failure The outlook has been enormously improved by treatment with adrenal steroids

Hypotonicity of Plasma

Transurethral resections of the prostate are usually carried out with intermittent washouts of the bladder and urethra with water. If much water is absorbed during this procedure there may be hæmolysis near the site of absorption, where the plasma osmolarity is grossly reduced; there is then hæmoglobinæmia and, occasionally, hæmoglobinuria, sometimes acute renal failure may develop

Thermal and Chemical Injuries

Patients with severe burns may develop hæmoglobinæmia and hæmoglobinuria from destruction of the red cells contained in or near the affected areas Acute renal failure occurs quite frequently and, though this is mainly due to renal ischæmia from the reduced blood volume, it is obvious that a superimposed hæmoglobinæmia will only make its development more likely

Arsine causes spherocytosis and acute hæmolysis Death from

...vere anæmia may come on in a few hours The gas is produced when ...rtain metals and acids containing arsenic come into contact

Other chemicals which sometimes cause severe hæmolysis and ...æmoglobinuria include naphthalene (moth balls), sulphonamides, and mephanesin.

Paroxysmal Cold Hæmoglobinuria

This condition is characterised by sudden attacks of hæmolysis which follow the cooling of a part or whole of the body It is due to an autohæmolysin which only becomes attached to the red cells at body temperatures below normal When such red cells circulate to some part of the body with a normal temperature they are hæmolysed Severe attacks are associated with rigors, fever and anæmia; acute renal failure does not occur

The disorder occurs in congenital and acquired syphilis, and sometimes follows certain acute infections such as " virus pneumonia "

HÆMOGLOBINURIA FOLLOWING HÆMOLYSIS IN THE URINE

If there is hæmaturia and the urine concentration falls below approximately S G 1 007 the red cells will hæmolyse and there will be free hæmoglobin in the urine This is only important as a diagnostic trap It will be recognised if the urine specific gravity is measured, and the deposit examined microsopically for red cells and casts

It has been reported that acute renal infarction may be associated with unilateral hæmoglobinuria

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PORPHYRIA

PORPHYRIA is a rare and often familial disorder of porphyrin metabolism which results in widespread abnormalities, particularly in the skin, gastro-intestinal tract and central nervous system Frequently there are acute exacerbations which may be associated with renal disturbances

Pathology

Porphyrins form part of the hæmoglobin molecule. In porphyria their metabolism is disturbed, so that their concentration in the blood rises and they are excreted in increased quantities both in the urine and fæces Several types of porphyrins are involved, but during an acute attack there is one, named porphobilinogen, which is always present in large amounts

Porphobilinogen is a colourless chromogen Its presence, however, can sometimes be suspected on naked eye examination of the urine, for its breakdown products on standing give the urine an orange or nectarine-like colour, this is usually overlooked, for it is confused with the appearance of a concentrated urine The presence of porphobilinogen is confirmed with Ehrlich's reagent (the same which is used for detecting the presence of urobilinogen) Both urobilinogen and porphobilinogen give a red colour within 20 seconds, they are then differentiated by adding chloroform, if the red colour remains outside

if it goes into the

ith an increased excretion of other porphyrins which may turn the urine dark purple.

At autopsy large amounts of porphyrins can be identified in the tubule cells These probably account for the disturbance of tubular function

Clinical Features of Acute Porphyria

Acute porphyria is often provoked by the administration of barbiturates Its main clinical features are abdominal pain, constipation, tachycardia, hypertension and peripheral neuritis Later, there may be coma, generalised flaccid paralysis and jaundice. In addition

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RENAL DISTURBANCES IN GOUT

Gout is characterised by a raised concentration of uric acid in the blood, and the deposition of sodium urate in bone, cartilage, joints and the kidney. The deposits in the kidney may cause death from renal failure.

Renal Function and Uric Acid Metabolism

Normally, only about 10 per cent of the uric acid that passes through the glomerulus is excreted in the urine, i e the greater part is reabsorbed The daily excretion of uric acid is approximately 1 g., it is very labile, for it depends on the content of cell nuclei in the diet

In gout there is evidence that there is an increased production of uric acid, and a compensatory increase in uric acid excretion, in an attempt to prevent its accumulation in the body An outstanding property of uric acid is that when its concentration rises above 7 mg per cent. it is in a supersaturated solution and is liable to sudden precipitation As the urinary excretion of uric acid increases, therefore, precipitation is liable to occur in the tubule lumen, and later, when the uric acid concentration in the blood rises, precipitation may also occur in the renal interstitial spaces.

As renal failure develops the urinary excretion of uric acid diminishes

Pathology

The changes in the kidney are due to:

1 Deposition of uric acid or its salts within the renal parenchyma.
2 Uric acid stones in the urinary pelvis and urinary tract.
3 Infection
4 Nephrosclerosis

Crystals of uric acid or sodium biurate are found in the tubular lumen and interstitial spaces Their presence is associated with necrosis of the tubules in the immediate vicinity of the deposits and local concentrations of chronic inflammatory cells. Occasionally the deposits can become sufficiently large to be macroscopically recognisable tophi, particularly in the tips of the pyramids

Pure uric acid stones are not opaque to X-rays, but usually they are covered with calcium salts and are readily identified. They may cause renal colic, hydronephrosis and complete destruction of the kidney

the most advanced cases develop an uncontrolled diuresis with extensive loss of sodium, potassium, chloride and water which may cause circulatory collapse and death.

Treatment

Prophylactic It is imperative that barbiturates (and possibly also sulphonamides) should not be given to patients who suffer from porphyria To make sure of this the patient should be given a card on which it is clearly stated that she is suffering from porphyria and that barbiturates must not be administered, however anxious and mentally disturbed the patient may appear

Curative Treatment is symptomatic; the electrolyte and water losses are replaced

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RENAL DISTURBANCES IN GOUT

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Renal infection follows the structural deformities caused by the uric acid deposition and stone formation.

The vascular lesions are those sclerotic changes found in chronic hypertensive vascular disease (p. 82); hypertension is not essential for their presence

Clinical Features

Evidence of renal abnormality may be confined to a trace of protein in the urine, or renal function may be so impaired that there is advanced renal failure The rate of progress of renal lesions is sometimes extremely slow, particularly if infection is well controlled In the absence of renal colic or hæmaturia the joint manifestations of gout often obscure the steady deterioration of renal function, and renal failure is only recognised in its terminal stages.

Treatment

The principles of treatment are to relieve joint pain during acute attacks and to eliminate the large accumulations of uric acid present in the body The treatment of the acute attacks is not relevant to renal gout

The high body content of uric acid is lowered by partially blocking its reabsorption by the tubules, thus increasing the amount excreted in the urine In this way a steady negative balance of uric acid of about 1 *g* a day can be produced, and if this continues for several months, all visible subcutaneous tophi will disappear It seems reasonable to suppose that interstitial deposits in the kidneys may also decrease in size, though there is the risk of an increased liability of uric acid deposition in the tubule lumen or the formation of urate stones In fact this risk appears to be negligible unless there is a previous history of renal stones and colic; such patients are given smaller quantities of urocosuric drugs and advised to drink large quantities of fluids When there is renal failure it is difficult to lower the blood urate level or to get rid of tophi

The following substances reduce tubular reabsorption of uric acid. salicylates, *acetylsalicylic acid, mercurial diuretics*, cinchophen, carinamide, and probenecid (Benamid). For prolonged treatment, either salicylates or probenecid are used

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RENAL DISTURBANCES IN MYELOMATOSIS

THIS disease is characterised by focal neoplastic proliferations of cells of the plasma cell series In about half the cases the urine contains unusual globulins and a protein of low molecular weight which has distinctive solubility properties and is known as Bence-Jones' protein It is possible, but it has not been demonstrated conclusively, that precipitation of this and other abnormal proteins is responsible for the obstructing renal casts which are often found in this disease.

Pathology

Multiple myelomatosis is associated with a variety of renal lesions, including renal infection from myelomatous tumours compressing the spinal cord, or *small collections of neoplastic myeloma cells within* the renal parenchyma, in addition renal amyloidosis occurs in 5–15 per cent. of all cases.

Many patients with myelomatosis, however, who die of renal failure show none of these changes; instead they develop the following structural disturbances. The most characteristic is the presence in the collecting tubules of dense laminated casts. Often these are surrounded by a ring of disintegrated tubular cells, the whole complex lying within a collecting tubule whose cells appear normal. In addition there is extensive tubular atrophy, but the glomeruli remain relatively unchanged Finally there tend to be multiple focal deposits of calcium in the casts, the tubule cells and the interstitial spaces The appearances suggest that much of the renal functional impairment is due to blocking of the collecting tubules.

Clinical Features

In the early stages, though proteinuria is frequently found, the non-renal clinical features of myelomatosis predominate The protein that is excreted is usually a mixture of albumin and globulin, whether or not Bence-Jones' protein is also present. The daily excretion of protein may be 15–20 g. Occasionally when there is an abnormal plasma globulin of small size it may appear in the urine without albumin ; this is characteristic of myelomatosis and can most easily be recognised by examining the urine electrophoretically

Bence-Jones' protein is identified by warming the urine; the protein at first comes out of solution and appears as a white precipitate, but as the urine becomes warmer the precipitate redissolves and the urine becomes clear If, however, other proteins are present, the persistent precipitate which they form on heating obscures the presence of Bence-Jones' protein To establish the presence of Bence-Jones' protein when other proteins are present it is therefore necessary to filter the urine immediately after it has been brought to the boil. The precipitated albumin and globulins will then be separated from the Bence-Jones' protein which remains in the clear filtrate. This filtrate is observed as it cools and Bence-Jones' protein will appear when the temperature falls to 70° C It is important that the warmed urine should not be allowed to cool before it has passed through the filter, for otherwise the Bence-Jones' protein is precipitated on the wrong side of the filter and does not appear in the filtrate To keep the urine warm it is best to filter small amounts at a time, to reheat the the urine at frequent intervals, and to place the filter paper upon a warm funnel. It is characteristic of multiple myelomatosis that if Bence-Jones' protein is present, it appears in large quantities; Bence-Jones' proteinuria is sometimes found in other conditions but only in small amounts

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Treatment

There is no treatment other than the relief of symptoms

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RENAL AMYLOIDOSIS

AMYLOID material consists of a combination of protein and chondroitin sulphuric acid which stains deeply with iodine, methyl violet and congo red. In certain conditions this substance is stored in large quantities, particularly in the liver, spleen, adrenal glands, intestine and the kidney.

Pathology

The kidneys are usually smooth, resilient and enlarged. The cut surface shows that both the cortex and medulla are broader than normal and the demarcation between them is sharp; the glomeruli can be identified as small translucent deposits which stain dark brown upon the addition of iodine. Occasionally there is considerable disorganisation, the kidneys are small and scarred and the cortex and medulla difficult to recognise.

Under the microscope amyloid material is found in the walls of all vessels, including the glomerular capillaries and the peritubular venous capillaries. In a renal biopsy specimen it is characteristic that the glomeruli may appear to be almost entirely replaced by amyloid material at a time when the glomerular filtration rate may be only moderately impaired. At autopsy the glomeruli mostly consist of solid, structureless, compact masses of amyloid of about the same size as a normal glomerulus. The amyloid material, which is laid in the peritubular venous capillaries, may be very thick but does not invade the tubule cells.

The tubule cells show the characteristic changes found in nephrotic glomerular nephritis, i.e. those changes found with heavy proteinuria, intracellular deposits of lipoid, and collections of an eosin-staining material of uncertain origin. Tubular atrophy is also present.

Without the use of special stains it is easy to confuse renal amyloidosis with diabetic nephropathy, chronic glomerular nephritis and particularly nephrotic glomerular nephritis.

Clinical Features

Amyloidosis was seen most commonly in sanatoria in patients suffering from chronic tuberculosis of the bones or lungs; it may,

however, occur as a complication of chronic sepsis from any cause and it is occasionally seen in rheumatoid arthritis and other diseases in which there is no sepsis

The first indication of renal amyloidosis is proteinuria, and the most common clinical manifestation is the development of a nephrotic syndrome This may be particularly severe, for the hypoproteinæmia may not only be due to proteinuria but also to a decreased rate of protein synthesis as a consequence of hepatic amyloidosis, and also to an impaired absorption of amino-acids because of amyloid deposits in the mucous membrane of the small bowel

Less often the presenting symptoms will be those of chronic renal failure, it is characteristic that the blood pressure may often remain normal for a considerable time after the onset

Diagnosis

The presence of amyloid material in the kidney is inferred if there is proteinuria, and amyloid is found in a gum or liver biopsy, it is confirmed by a renal biopsy. A negative liver biopsy does not exclude renal amyloidosis

As congo red dye is absorbed by amyloid, the finding that a patient retains the dye after its intravenous administration is sometimes a useful indication of amyloidosis An injection of 1 ml of a 1 per cent solution of congo red for every 10 lb of body weight is given intravenously, and samples of venous blood are then taken at, 2, 4, 6, 30 and 60 minutes thereafter The line drawn through the values at 2, 4 and 6 minutes which exterpolates the plasma concentration at 0 time gives the theoretical concentration at the time of the injection At 30 minutes, less than 32 per cent of the dye should have disappeared from the circulation, and at the end of an hour less than 51 per cent, with amyloidosis 68 to 91 per cent has disappeared at the end of 30 minutes, and 77 to 100 per cent at the end of an hour.

Treatment

If the disease with which amyloidosis is associated can be controlled, particularly if a septic lesion can be excised, the amyloid deposits may resolve, renal function will improve, and the blood pressure will return to normal Otherwise treatment is symptomatic and is that of the nephrotic syndrome (p 90) and chronic renal failure (p 134)

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SCLERODERMA

The generalised form of scleroderma not only affects the skin but also the gastro-intestinal tract, the lungs, the heart and the kidney

Pathology

The renal lesion is exceedingly uncommon The kidneys are swollen and pale, while the cut surface shows a mottled congestion of the cortex which is due to patchy cortical necrosis

Histologically there are focal areas of cortical necrosis which are caused by two characteristic arterial changes. The intima of the intralobular arteries is grossly thickened with concentric layers of a "mucoid" substance which nearly occludes their lumens; while many of the afferent glomerular arteries and distal parts of the intralobular arteries are necrosed, isolated polyarteritic lesions and "wire-loop" lesions have also been described, but both changes are inconstant

Clinical Features

In general, scleroderma is a slowly progressive disease, but once it has affected the kidney death from renal failure usually occurs within a few weeks. There is proteinuria, a rising blood urea and coma, some of the cases have a terminal onset of hypertension with convulsions

Sometimes the development of the renal lesion appears to have been provoked by the use of adrenal steroids when these have been used to alleviate some of the other symptoms of scleroderma.

Treatment

Treatment is symptomatic.

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RADIATION NEPHRITIS

RADIATION nephritis has only been described in patients with malignant tumours of the testicle following irradiation of the periaortic abdominal glands.

Pathology

There is little to see with the naked eye except some fibrous tissue between the kidney and the peritoneum. The capsule, however, is free and the kidney normal in size.

Microscopically the capsule shows considerable fibrous thickening. The glomeruli are smaller than normal and the glomerular loops show replacement with variable quantities of an eosin-staining material. Many of the tubules are atrophic and they are separated by large amounts of intertubular material which in some places includes fibrous tissue

The larger vessels show no changes, the intralobular arteries and the arterioles may show sclerotic changes (p. 82), and the glomerular capillaries occasionally show necrotic lesions similar to those found in malignant hypertension (p 82). These necrotic lesions may be present in the kidney even though they are absent from other organs, and the patient has not suffered from malignant hypertension clinically.

Following irradiation of the kidneys in animals the blood pressure rises before any abnormal microscopical changes are evident. It seems probable, therefore, that the vascular lesions that are seen later are due to the hypertension, the cause of the hypertension is unknown.

Acute Radiation Nephritis

Clinical Features

The onset of symptoms attributable to changes in the kidney occurs after a latent period of six to twelve months from the start of radiotherapy The reason for this interval is not known; it is one of the most interesting points about the disease.

Symptoms develop gradually; they include oedema, dyspnœa, hypertension, headache, nausea and vomiting, lassitude, and nocturia In most instances the patient has to retire to bed within a month. There is no clear-cut acute nephritic syndrome or nephrotic syndrome.

The condition usually appears as chronic renal failure of rapid onset. In all cases there is proteinuria and hypertension, but widespread oedema and cardiac failure seem rather to follow a hypertension of increasing severity than to be an integral part of the initial disturbance. Proteinuria is rarely greater than 5 g./day and hypoproteinæmia has not been recorded. Some degree of renal failure occurs in all cases and is characteristically associated with severe anæmia.

Course

A third to a half of the cases reported in one series died within 4–12 months of the onset of symptoms. Death was due to hypertensive cardiac failure, hypertensive fits and renal failure. The remainder survived, but continued to have proteinuria, hypertension and some diminution in glomerular filtration rate.

Prognosis

A rise in blood urea above 200 mg. per cent. at some time during the first three months or the development of pleural effusions without generalised oedema are stated to be signs indicative of a poor prognosis. The duration of the latent period, the age of the patient, and the height of the blood pressure in the first five months, have no prognostic significance.

Treatment

Prophylactic. With the greatest care, the dose of X-rays needed for secondary seminomas is perilously close to that which can damage the kidney. In future the use of the cobalt bomb should enable the field of irradiation to be so narrowed that renal damage, if it occurs, is limited to one kidney and the damaged kidney can then be removed.

Curative. It is imperative to decide if the renal damage is unilateral or bilateral, for if it is unilateral the blood pressure can be lowered by nephrectomy.

Otherwise treatment is symptomatic and includes the control of hypertension, cardiac failure, oedema and renal failure. The necessity for blood transfusions appears to be greater than in other forms of renal failure; their administration is frequently accompanied by generalised reactions.

Chronic Radiation Nephritis

Some patients never develop a period of acute renal disorder, but 18 months to several years after irradiation they are found to be suffering from what appears to be "chronic glomerular nephritis." They have proteinuria, hypertension and some impairment of renal function.

The cause of this form of radiation nephritis is obscure. Some cases have shown no tendency to further deterioration.

Malignant Hypertension

Occasionally there is a sudden onset of malignant hypertension. It may or may not be accompanied by renal failure. Death occurs within a few weeks.

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CONGENITAL, MACROSCOPIC, STRUCTURAL LESIONS OF THE KIDNEY

The term "macroscopic" is inserted in the title of this section in order to exclude the congenital microscopic structural lesions of the tubules which are associated with innate functional defects (p 160) Bell's classification of these malformations is as follows:

Renal agenesis
- (a) Bilateral
- (b) Unilateral.

Renal hypoplasia:
- (a) Bilateral hypoplasia
- (b) Unilateral dwarfed kidney

Renal ectopia

Anomalies due to fusion:
- (a) Horseshoe kidneys
- (b) Unilateral fused kidney, crossed renal ectopia

Duplication of pelvis and ureter

Cystic disease of the kidneys
- (a) Polycystic kidneys
- (b) Solitary cysts

RENAL AGENESIS

Bilateral Agenesis

Bilateral agenesis is not compatible with life, though occasionally the infant may live for two to three days Not only are the kidneys absent but the ureters are often rudimentary Other congenital abnormalities, such as spina bifida, are always present

Unilateral Agenesis

Unilateral agenesis (Fig 72) is more common than bilateral agenesis and may not be discovered until autopsy for some other disease It occurs equally in both sexes and is more frequent on the left side The remaining kidney hypertrophies and often weighs as much as a normal pair of kidneys

Other congenital abnormalities may be found, in children gross

abnormalities, such as meningocœle are not infrequent; in adults they are found less often *and occur mainly in the genital* tract, for instance, there may be a bicornuate or a double uterus.

RENAL HYPOPLASIA

Bilateral Hypoplasia

Bilateral hypoplasia usually causes *death shortly after birth* *Very* rarely it may produce a state of chronic renal failure after two to three years of life

Unilateral Hypoplasia

Unilateral hypoplasia has to be differentiated from acquired unilateral disease, for chronic urinary obstruction or infection may also result in a remarkably small kidney. As this differentiation is sometimes very difficult, the term *unilateral dwarfed kidney* is used to include *those kidneys which are unequivocally* hypoplastic and those in which hypoplasia is the most likely diagnosis

By combining the incidence of unilateral agenesis and hypoplasia, Bell has calculated from his autopsy records that in persons over one *year of age the chance of there being only one kidney capable of* sustaining life is about 1/200

RENAL ECTOPIA

Ectopic kidneys are usually situated either in the iliac fossæ, including the brim of the pelvis, or in the pelvic cavity (Fig. 71) They *occur equally in the two sexes, and are rather more common on the left* side In the iliac fossæ they show no major structural alteration, but when they are in the pelvis they may be seriously distorted Frequently the kidney is hypoplastic; the renal pelvis is usually directed forward and the ureter is often dilated and tortuous The renal artery arises from the nearest part of the aorta or the common iliac artery.

Ectopic kidneys may function normally, but they are liable to hydronephrosis and pyelonephritis

Clinical Features

Lower abdominal pain or discomfort, dysuria, frequency and hæmaturia are the presenting symptoms; or proteinuria may be found during a routine examination Occasionally an ectopic kidney may first be diagnosed during pregnancy and may be confused with a tumour or pelvic abscess, an intravenous pyelogram allows the right diagnosis to be made only if the kidney can excrete the radio opaque

material, at other times a retrograde pyelogram or laparotomy is necessary

Often there are other congenital abnormalities.

Movable Kidney

The mobility of the kidney may be greater than normal but it is extremely doubtful if excess mobility is ever the cause of symptoms, or makes the kidney more liable to infection or other disorders At one time, however, numerous operations were performed to secure errant kidneys into more conventional sites Most of the operations

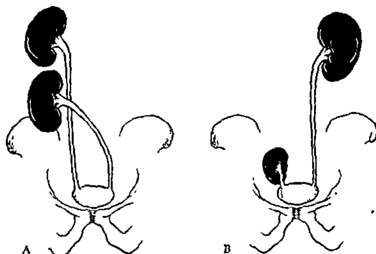


FIG 71 Renal ectopia (a) Both kidneys on the same side, and (b) Unilateral pelvic kidney

were performed in that notorious group of middle-aged women who complain of vague abdominal pains.

ANOMALIES DUE TO FUSION

Horseshoe Kidney

This malformation consists in the fusion of two poles of the kidneys, usually the lower poles, across the midline The two pelves are always separate and point in a forward direction, the two ureters travelling anteriorly over the surface of the lower poles (Fig. 72)

Horseshoe kidneys occur more frequently in males, and in persons over one year of age Bell found the incidence to be 1 400 There is no

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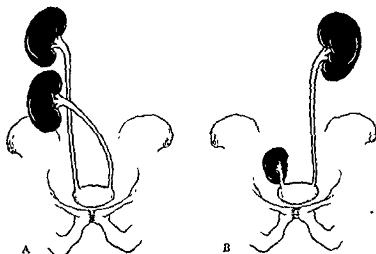


FIG 71 Renal ectopia (*a*) Both kidneys on the same side, and (*b*) Unilateral pelvic kidney

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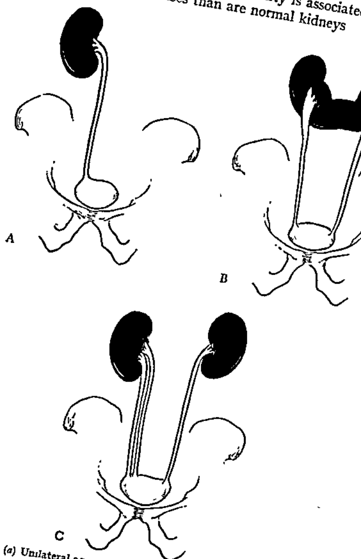


FIG 72. (a) Unilateral agenesis, (b) Horseshoe kidney, (c) Double ureter

Unilateral Fused Kidney

Very rarely both kidneys may be fused together on one side of the body. Both ureters enter the bladder in their normal sites, so that one ureter has to travel across the midline and is thus more liable to cause hydronephrosis and infection.

DUPLICATION OF PELVIS AND URETER

This anomaly is more common in women and is found most frequently on the left side; it is not unusual for it to be bilateral, when it is more extensive on one side than the other. The two ureters from one kidney may be completely separate in their course to the bladder, so that there are two ureteric orifices to one side of the midline (Fig. 72) At other times the two ureters fuse together either in the bladder wall or somewhere between the pelvis and the bladder Occasionally one ureter may enter the vagina, the urethra, the seminal vesicles or the vas deferens

Duplication of the pelves and ureters is often associated with pain, hydronephrosis and recurrent urinary infection

CYSTIC DISEASE OF THE KIDNEYS

A malformation which may be unilateral or bilateral. Bilateral cystic disease of the kidneys is far more frequent and important clinically.

Bilateral Polycystic Kidneys

This is a familial condition which declares itself clinically either in infancy (the neonatal form), or in middle age (the adult form), in childhood and up to the age of 20 the incidence falls off to negligible proportions The reason for this remarkable division of incidence is not known. It is possible that the two forms of the disease, though they appear almost indistinguishable structurally, may stem from different ætiologies. In favour of this theory is the fact that the adult form appears to be inherited as a Mendelian dominant in families in which there are a number of other cases, whereas the neonatal form occurs in infants derived from stock in whom the disease has never previously appeared. There are no records of adult and neonatal cases occurring in the same family.

Both forms occur equally between the two sexes

Pathology

Both kidneys tend to be considerably enlarged, though the degree of enlargement may be unequal (Fig 73) Each consists of a compact mass of cysts. On section the cysts are seen to be scattered equally in the cortex and medulla, and usually there does not seem to be any intact parenchyma On rare occasions the cysts may be limited to one pole In the neonatal disease all the cysts tend to be of a similar size, whereas in adults they vary considerably and some may be exceedingly large

The cysts are filled with a watery fluid which may be clear, blood-stained from recent hæmorrhage, or brown from an old hæmorrhage; some may be filled with pus. They are lined by a single layer of epithelium and occasionally a normal glomerular tuft may be found invaginated into the cavity of a cyst, when the cyst is then considered to be the distended capsular space of that glomerulus Cysts do not often communicate with the pelvis of the kidney.

It can be demonstrated that the contents of some cysts are in a continuous flux with the circulation, e g. inulin placed in the cysts will

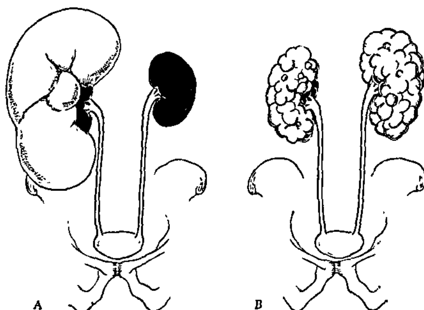


FIG. 73 (*a*) Solitary cyst, (*b*) Polycystic kidneys

appear in the blood and vice versa. It has been suggested therefore that the cysts have some renal " functional " capacity, however trivial Unless the cysts are joined to the pelvis, however, this is of no consequence whatever its extent.

Pathogenesis

The normal nephron develops in two stages The ureteric bud grows upwards and, after widening out as the pelvis and calyces, it invades the metanephros, where it divides into collecting ducts; these penetrate deeper and, finally, each comes to rest against a solid curved shelf of metanephric cells which cover the tip of the collecting tubule bud. Each such collection of metanephric cells then arranges itself

around a lumen in continuity with the collecting duct, and gradually the rest of the nephron is developed i e the distal tubule, the loop of Henle and the proximal tubule (known collectively as the convoluted tubule) and, finally, the glomerulus. Very early in embryonic life these convoluted tubules often become detached from the collecting ducts; their lower ends becoming blocked and the tubule cystic. Normally these cysts atrophy, and another convoluted tubule is formed whose lumen is continuous with, and remains attached to, the original collecting tubule.

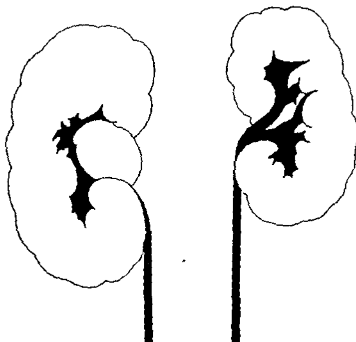


FIG 74 Polycystic kidneys An intravenous pyelogram, illustrating the distortion of the pelvis and calyces by the cysts

It is considered that polycystic kidneys may be due to a persistence of those early, normally occurring fœtal cysts which in normal circumstances atrophy and disappear

Clinical Features

Neonatal form. Usually neonatal bilateral cystic kidneys cause stillbirth, and sometimes their size may cause serious difficulties during delivery The infant may live for a few months or one to two years, only to succumb to chronic renal failure

Adult form. The onset of the presenting symptoms usually occurs when the patient is about 45 years old. These may be entirely renal with hæmaturia, clot colic, or acute pyelonephritis, or they may be more generalised, when they are due to renal failure or hypertension Sometimes the patient complains of abdominal distension, or pain following some relatively minor trauma. Proteinuria is always present and may be the first abnormality to draw attention to the renal disease.

Hypertension develops in only about 75 per cent. of cases and is rarely malignant.

By the time the patient begins to complain of symptoms the kidneys are usually easily palpable and have a characteristic "knobbly" feel. The diagnosis is confirmed by an intravenous pyelogram which shows the pelvis to be elongated with the calyces stretched out, and their peripheral ends shaped into crescents of varying sizes (Fig. 74). Early disease showing only unilateral abnormalities may be difficult to differentiate from solitary cysts or a tumour.

Prognosis

Death is due either to chronic renal failure from compression of the renal parenchyma by the enlarging cysts, and chronic renal infection; or from hypertensive cardiac failure, and cerebrovascular accidents. Hypertensive cardiac failure is the most common immediate cause of death

Before the introduction of antibiotics the average age at death was about 55 years, i e the average duration of the disease once it had become manifest was 5–10 years. There are exceptions to these averages, however, and if renal infections are promptly treated some patients live many years without appearing to deteriorate.

Treatment

If the disease is almost confined to one kidney which is subject to recurrent infections and is functionally useless it may be wise to remove it, after first establishing that the function of the other kidney is adequate

When the disease is bilateral the only measure which may cause any improvement is the evacuation of some of the larger cysts in order to relieve the pressure upon the residual parenchyma. The functional results of such operations, however, have not often been investigated; attention has been paid rather to the improvement in appearance of the intravenous pyelogram, and the continued survival of the patient. Until now there has not been a convincing demonstration that the operation will in fact prolong life; and some authorities categorically deny that renal function is improved. Nevertheless, there is general

agreement that the operation is sometimes most useful in the relief of recurrent pain and hæmaturia and that occasionally there has been relief of hypertension. It is considered that the operation should only be performed on one side at a time, for there is often a relatively severe transient post-operative deterioration in renal function.

Otherwise, treatment is symptomatic and is that of renal failure, renal infection, hypertension and cardiac failure.

Solitary Renal Cysts

Small cysts are frequently found during routine autopsies, their size usually precludes them from having caused any ill effects

Large "solitary" cysts are rarely single, but occur in clusters of two or three (Fig 73). They are more common on the right side, and more often seen in women They may be situated in either pole, or in the middle of the kidney, nearly always they spring from the parenchyma, but occasionally they may be entirely sub- or extra-capsular. The parenchyma near the cyst is always considerably compressed. They only rarely have a connection with the pelvis The contents of the cysts contain 500–1,000 ml of yellow or blood-stained fluid and sometimes considerably more The walls of the cysts are composed of thin fibrous tissue in which a few atrophic tubules may be seen.

Clinical Features of Large Cysts

The main complaint is of intermittent attacks of abdominal pain interspersed by long remissions. The attacks tend to become more frequent as the years go by and the total duration of the history may be 20–30 years. The pain may be associated with fever, dysuria and occasionally with hæmaturia Painless hæmaturia is sometimes the first symptom

Cysts in the upper poles are particularly difficult to palpate and when on the right side may cause symptoms resembling cholecystitis Lower-pole cysts cause gastric and intestinal symptoms, with nausea or diarrhœa, they are also liable to obstruct the ureter and cause renal infections.

The diagnosis should be evident from an intravenous pyelogram, [illegible]

Treatment

This is surgical. If possible, a heminephrectomy is performed, otherwise a total nephrectomy is necessary.

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Appendix 1

DIURETICS

A DIURESIS is defined as an increase in the flow of urine, and a diuretic is therefore a substance which increases the flow of urine On this basis water, alcohol, dextran and, in some circumstances, adrenal steroids and digitalis, are all diuretics For clinical purposes, however, it is customary to confine the term to those substances which (1) produce their effect by a direct action on the kidney, and (2) not only increase the flow of urine but also increase the urinary output of sodium chloride In conformity with this tradition only the following diuretics will be discussed

- Organic mercurials
- Acetazoleamide (Diamox)
- Xanthine derivatives
- Aminometradine (Mictine)
- Acidifying salts
- Osmotic diuretics

It must be emphasised that when the flow of urine is increased with one of these substances it is not evidence that renal function has been improved. In acute renal failure, for instance, it is quite possible to increase the flow of urine with an osmotic diuretic, but it is a meaningless and misleading manœuvre which is more likely to do harm than good (p. 120) The best use for diuretics is to mobilise accumulations of oedema fluid.

Organic Mercurials

These are by far the most consistently effective diuretics.

Mode of Action

Organic mercurials are rapidly excreted by the tubules Their presence in the tubule cell inhibits the tubular reabsorption of chloride ions, and this automatically increases the urinary excretion of an equivalent quantity of cations, particularly sodium and potassium. There is thus an increased output of total solutes, so that an osmotic diuresis is finally responsible for the increase in urine flow (p 42)

The effectiveness of mercurials is greatly diminished when the glomerular filtration rate is very low, even though the total number of nephrons is relatively normal (e g, in cardiac failure) It is possible that so little chloride is filtered that variations in the amount

reabsorbed produce little effect on the total excreted. Mercurials are also relatively ineffective in chronic renal failure.

On the other hand, the effect of mercurials is greatly enhanced by the simultaneous administration of ammonium chloride. This combination produces an effect which is usually far greater than the sum of both when given separately. The reason is not at all clear. It is not related to changes in blood *p*H. It may be related to the greater quantity of chloride present in the body needing evacuation. Even this explanation is precarious, for the enhancement occurs even when the concentration of plasma chloride remains unchanged, when it is difficult to explain how the kidney is aware that more chloride is present.

The relative quantities of chloride, sodium, potassium and water which are excreted in response to mercurials vary; occasionally more solutes than water are excreted and the patient's body fluids become *either acutely or chronically hypotonic (i.e. overhydrated); at other* times the excretion of chloride is demonstrably greater than that of sodium and potassium, and an alkalosis develops; alternatively there may be potassium deficiency. These electrolyte imbalances tend to impair the diuretic effect of subsequent doses of mercurials.

Administration

The following preparations are in common use:

Name	*Route of administration*	*Dose*
Mercaptomerin (Thiomerin)	Subcutaneous Intravenous	0 5–2 ml
Meralluride (Mercardan) (Mercuhydrin)	Subcutaneous Intravenous	1–2 ml
Mersalyl*	Intramuscular Intravenous	1–2 ml 1–2 ml (in 10 ml of water)
Mercuramide* (Neptal)	Intramuscular Intravenous (Different dilution)	1–2 ml. 5 ml
Chlormerodrin (Mercloran) (Neohydrin)	Oral	1–6 tablets

* Both these preparations contain theophylline.

The older mercurials such as mersalyl and mercuramide (Neptal) are highly irritant and can only be given as a deep intramuscular injection or intravenously; they are apt to cause pain at the site of injection, and if some escapes into the subcutaneous tissues there may

be necrosis of the skin Mercaptomerin (Thiomerin) and meralluride (Mercardan) are less irritant and, as they can be given subcutaneously and rarely cause pain, they can be self-administered; they are gradually replacing the older preparations.

Treatment is begun with one of the parenteral preparations, 1 ml being given either subcutaneously or intramuscularly on alternate days; the amount is increased up to 2 ml. subsequently, if necessary *In order to lessen the need for mercurials a low-salt diet is given, and* to increase the diuresis ammonium chloride 3–9 g is given per day, potassium chloride 1–3 g per day is also given to avoid potassium deficiency. If there is no response some authorities use one or more intravenous injections to initiate a diuresis Subsequently subcutaneous or intramuscular injections are given on alternate days until there is no further fall in weight, when the injections are either discontinued or given less frequently

The oral preparation is only used to prevent reaccumulations of oedema; in large doses it is apt to cause gastric symptoms, in mild cases it is sometimes of value and allows routine injections to be more widely spaced.

The use of acetazoleamide (Diamox) or theophylline ethylenediamine (Aminophylline) in conjunction with mercurials is discussed below.

Complications

1. On rare occasions an intravenous administration may cause sudden death from ventricular failure

2 Equally rarely, the frequent administration of an organic mercurial may lead to an accumulation of mercury, particularly in patients with poor renal function There may be stomatitis, diarrhœa, anæmia and mental changes Treatment is with BAL

There have been a few reports of elderly men suffering from ischæmic heart disease who have developed a nephrotic syndrome following the prolonged use of mercurials. In some cases an increased urinary excretion of mercury has been demonstrated and, histologically, renal biopsy shows dilated tubules with thin atrophic tubule cells, appearances compatible with mercury poisoning

3 Sensitivity reactions are far more common and include fever, erythematous rashes, urticaria, pruritus, exfoliative dermatitis, abdominal pains, backache, headache, vomiting and diarrhœa, a transient agranulocytosis has also been reported Sometimes these [illegible] Anti-

Alkalosis only occurs when ammonium chloride is not given.

Chronic overhydration occurs in a patient who has had mercurial injections for a considerable time and in whom it no longer produces a diuresis. *Acute overhydration* follows a brisk initial diuresis and is recognised by the diminishing response to each mercurial injection, increasing oliguria and weight gain, rising blood urea, nausea and vomiting. Both forms respond to the intravenous administration of hypertonic saline (p 150).

In exceptional cases a diuresis may be so extensive and rapid that the patient develops some of the symptoms of *acute circulatory distress* with hypotension, dizziness, sweating and tachycardia. This is seen particularly in patients with a nephrotic syndrome; it does not occur with cardiac failure Treatment consists in raising the foot of the bed.

Potassium deficiency may follow prolonged courses of mercurials; again there is a diminishing response to each injection, and in patients with cardiac failure the degree of failure may become more marked Diagnosis is difficult, for the plasma potassium concentration is a poor guide to the total body potassium (p 151) The daily prophylactic administration of potassium chloride should prevent this complication

5 Some elderly patients with prostatic enlargement may be caused serious difficulties when there is a sudden and extensive diuresis, for a rapid overdistension of the bladder may lead to acute retention of urine.

Acetazoleamide (Diamox)

This substance has many therapeutic uses, as a diuretic it is sometimes combined with a mercurial

Mode of Action

Acetazoleamide is a carbonic acid anhydrase inhibitor, and its effect on renal function, therefore, is to diminish the production of hydrogen ions by the tubules (p 45). It follows that tubular reabsorption of sodium is decreased while tubular secretion of potassium is increased (p 54). The net result is an increased excretion of sodium and potassium, a fall in plasma bicarbonate and a tendency towards a metabolic acidosis As the plasma bicarbonate falls the efficiency of acetazoleamide as a diuretic rapidly diminishes

Administration

The drug is given by mouth in doses of 0 25–1 0 g. once a day, preferably in the morning Because of its tendency to cause a metabolic acidosis which then interferes with its action, acetazoleamide is usually given intermittently, either on alternate days or for two to three days at intervals of a few days. Daily administration, however, is sometimes

successful presumably because the effect of the drug may only last 6–12 hours, and before the next dose is given a sufficient readjustment in the plasma concentration of bicarbonate has taken place.

Acetazoleamide is occasionally useful in patients who have become refractory to mercurials, but its widest use is in combination with them, for though both drugs produce their effect by inhibition of tubular reabsorption, one has its primary effect on chloride ions and the other on sodium ions The mercurials tend to produce a metabolic alkalosis which enhances the effect of the acetazoleamide, while the acetazoleamide tends to produce a metabolic acidosis which enhances the effect of the mercurial The drugs are therefore given on alternate days so that each may compensate for the effect of the other. In these circumstances ammonium chloride must not be given with the mercurial. A mixture of potassium chloride and bicarbonate should be given to prevent potassium deficiency, for both mercurials and acetazoleamide may substantially increase the urinary excretion of potassium.

Acetazoleamide can be given to prevent the reaccumulation of oedema; it may be sufficient by itself or its administration may allow mercurial injections to be given less frequently. Prolonged treatment may be associated with the formation of renal calculi.

Xanthine Derivatives

With one exception these substances are now rarely used as diuretic agents

Mode of Action

[illegible]

excretion This second effect is most marked with theophylline ethylenediamine (Aminophylline) The total increase in salt and water excretion, however, is inferior to that obtained with a mercurial or acetazoleamide

Administration and Side Effects

[illegible]

have been ineffective; 0.5 g is given once or twice a day on the days

of mercurial injections. The success of this combination is thought to be due to the increased amount of chloride that is presented to the tubule by the rise in glomerular filtration rate.

Aminometradine (Mictine)

This new oral diuretic is being increasingly used, particularly for prolonged treatment

Mode of Action

Tubular reabsorption of sodium is impaired by an unknown mechanism.

Administration and Side Effects

The advantage of this substance is that it can be given by mouth. The dose is 200 mg once to four times a day. Headache, anorexia and nausea may occur when 600 mg or more is given per day The incidence of these side effects is less with intermittent administration, e g on alternate days, or for two to three days every few days.

Aminometradine is most useful in preventing the reaccumulation of oedema fluid in chronic cardiac failure.

Acidifying Salts

Ammonium chloride is the only acidifying salt that is commonly used as a diuretic

Mode of Action

It has been pointed out earlier (p 51) that when ammonium chloride is metabolised, hydrogen and chloride ions are released They *are promptly excreted and at first the chloride in the urine is accompanied* by an increased excretion of sodium. The increase in solute *output and water excretion of ammonium chloride administration are* therefore due to a brisk sodium chloride osmotic diuresis. After the first day, *the administered chloride is excreted with hydrogen* and ammonium ions produced by the kidney, and the initially high rate of sodium excretion *returns to normal (Fig. 27). It follows that after* the first two or three days the administration of ammonium chloride *no longer mobilises sodium, there continues* to be a mild osmotic diuresis, but this only produces a minimal increase in sodium excretion (see below).

Administration and Side Effects

Ammonium chloride is given orally in doses of 1–3 g. 6–8-hourly. The usual preparations are *enteric-coated* tablets, but these are

occasionally passed intact in the fæces. Capsules, however, are liable to cause nausea and vomiting. The best preparation is a simple aqueous solution though it has an unpleasant taste

By far the most important use of ammonium chloride is in combination with a mercurial. It is occasionally used by itself when only a short-acting diuretic is needed, e g. in the treatment of premenstrual "tension."

Osmotic Diuretics

An osmotic diuresis is always accompanied by a moderate increase in the excretion of sodium chloride and water, but the increase varies with the initial rate of salt excretion and the extent of the osmotic diuresis In an oedematous patient excreting small quantities of sodium, only a very large osmotic diuresis is sufficient to increase adequately the urinary salt excretion But the administration of large amounts of an osmotic diuretic is a cumbersome, sometimes unpleasant, and relatively unrewarding procedure, for these reasons osmotic diuretics are now hardly ever used for therapeutic purposes

The following substances have been used urea, potassium salts, glucose, *sucrose and mannitol*

Urea

In order to obtain a reasonable osmotic diuresis it is necessary to give 10–20 g of urea by mouth two to three times a day The taste of urea is bitter and unpleasant and only poorly masked by fruit juices

Potassium Salts

Potassium chloride, bicarbonate, acetate, and citrate have all been

for this purpose.

Glucose, Sucrose and Mannitol

large quantities of glucose and is not a practical procedure.

Occasionally *in an* oedematous diabetic patient the urinary excretion of glucose may be allowed to rise when trying to mobilise oedema fluid.

Sucrose and Mannitol These must also be given intravenously. When given by this route neither is metabolised, so that smaller

quantities are needed to produce a diuresis than when glucose is used. The usual solutions contain 50 per cent. sucrose, or 25 per cent. mannitol, 100–200 ml are given. These hypertonic infusions are apt to cause pain in the vein and thrombophlebitis.

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Appendix 2

DIETS

High Protein, Low Sodium Diet

Protein Content 180–190 g
Sodium Content 30–40 mEq

Meal	oz	g.	*Food*	*Protein* g	*Sodium* mEq
Breakfast	5	142	Porridge	2	0·3
	2	57	Unsalted bread	4	0·2
	½	14	Unsalted butter or margarine	—	0·2
	4	114	2 eggs, cooked in any way	14	6·6
			Milk from daily allowance for porridge and tea or coffee		
			Sugar as desired	—	—
	½	14	Marmalade, honey or jam	—	0·2
Dinner	5	142	Lean meat, cooked weight	35	4·1
	4	114	Potatoes, boiled, roasted or fried	2	0·2
			Vegetable or salad, average helping	0·5	0·5
			Stewed or tinned fruit, average helping	0·5	0·5
			Pudding using high protein Edosol milk from daily allowance		
Tea	2	57	Unsalted bread	4	0·2
	½	14	Unsalted butter or margarine	—	0·2
	2	57	Lean meat as sandwich filling	14	2·2
			Tea with milk from daily allowance		
			Sugar as desired		
	1	28	Cake made from low sodium ingredients (see general instructions)	2	0·4
Supper	6	170	Fried fish (cooked weight)	35	12·0
	4	114	Potatoes, boiled, roasted or fried	2	0·2
			Vegetable or salad, average helping	0·5	0·5
			Fruit, average helping	0·5	0·5
			Pudding using high protein Edosol milk from daily allowance		
Daily	4	114	Ordinary milk for tea	4	2·5
	25	710	Edosol milk reconstituted +	25	1·1
	1½	43	Casilan for drinks and puddings	33	1·8
				184	34·4

All foods cooked without salt

In this diet, if ordinary milk is substituted for Edosol the sodium will rise by 14·6 mEq, and if ordinary bread and butter are substituted for the low sodium varieties the sodium will rise by 22 mEq

General Instructions

Edosol is a low sodium synthetic milk powder made by Trufood reconstituted according to the directions on the tin Casilan is a calcium caseinate, a 90 per cent. soluble protein made by Glaxo.

The mixture of Edosol and Casilan can be used in place of ordinary milk to make cereal milk puddings, custard, egg custard, milk jelly, as well as in drinks flavoured with milk-shake syrups, coffee and malted drinks It is not suitable for use in tea

To make a low sodium diet interesting, use pepper, mustard, vinegar, lemon juice, home-made unsalted chutney and pickles Herbs such as bay leaves, thyme and sage, and spices such as curry, cayenne pepper, paprika, cloves and nutmeg To improve the flavour fry potatoes and other vegetables, toast the bread and use garlic and onions liberally.

Foods low in sodium not mentioned previously.

Most frozen vegetables

Lard, dripping, olive oil, dairy cream, Matzo, Rakusen's unsalted crackers, shredded and puffed wheats, unsalted yeast extract made by Marmite

Low sodium canned peas and baked beans in tomato sauce are obtainable through Boots

Recipe for low sodium baking powder, for use with plain flour:

Starch . . .	28 g
Potassium bicarbonate . .	40 g
Tartaric acid . . .	8 g
Potassium bitartrate . . .	56 g.

This recipe can be made up by any chemist It should be used like ordinary baking powder

Avoid

All bread if not specially made without salt
Crispbreads such as Ryvita, cream crackers
Ordinary cakes and biscuits
Self-raising flour
Cornflakes
Smoked, tinned and shell fish
Shop-prepared meats and pies, tinned meat, sausages, bacon, ham, mea and fish pastes
Cheese, except home-made unsalted
Salted butter and margarine
Tinned vegetables, tinned tomato juice
Tinned soups, shop pickles, sauces, salad cream
Meat and yeast extracts Golden syrup Rennet
Chocolate and toffees above 1 oz. per day
Sodium bicarbonate "Health salts" Liquorice
Beer, over ½ pint daily

Low Protein Normal Sodium Diet

Protein Content 30 g

Meal	oz	g	*Food*	*Protein* g.
Breakfast	5	142	Porridge or	
	1	28	Cornflakes	2
	1	28	Bread, plain or toasted—1 slice from a cut loaf	2
			Butter or margarine	
			Marmalade, honey or jam	
			Tea with sugar and lemon or coffee with sugar	
Dinner	1	28	Meat or cheese or	
	1½	43	Fish or	
	2	56	Egg	7
	1	28	Bread or	
	4	114	Potato—1 medium sized, fried if desired	2
			Vegetables or salad, average helping, not including peas or butter beans	0 5
			Fruit, average helping, raw or cooked with sugar	0 5
Tea	1	28	Bread	2
			Butter or margarine	
			Jam or Honey	
			Tea with sugar and lemon	
Supper or High Tea			As Dinner	10
Daily	4	114	Milk—8 Tablespoons	4
				30

Alternatives

1	28	Biscuits, most kinds	2
3	84	Boiled rice (or 1 oz (28 g) of raw rice)	2
1	28	Cake, average	2
1	28	Pastry, short	1
1	28	Pastry, flaky	1 5
1	28	Custard, made from powder	1
1	28	Jelly, prepared	0 5
1	28	Dairy cream	0 5
1	28	Shelled peanuts	8
1	28	Brazil or walnuts	4
1	28	Butter beans, haricot beans, tinned peas	2
1	28	Milk chocolate	2
1	28	Plain chocolate	1 5

Sugar, glucose, jam, marmalade, honey, fruit squashes, boiled sweets, peppermints, butter, margarine, lard and other fats can be eaten in unlimited quantities To increase the calorie content of the diet add fat to vegetables or fry them, and use extra sugar, glucose or lactose on fruit and in drinks Glucose and lactose are less sweet than sugar and can therefore be taken in larger quantities

Foods High in Potassium and Low in Protein

Food		Potassium mEq /100 gram
Cereals	All Bran	24 5
	Malt bread	9 5
	Ryvita	12 0
Fruit and nuts	Apricots—dried, stewed	20 0
	Apricots—tinned in syrup	6 6
	Bananas	8 9
	Dates	19 3
	Figs—dried, stewed	14 8
	Grapes—black	8 1
	Prunes—dried, stewed	8 5
	Chestnuts—shelled	12 7
Vegetables	Beetroot, boiled	9 0
	Mushrooms, fried	14 5
	Potatoes, old and new boiled	8 4
	Potatoes, baked in skin	17 4
	Potatoes, roasted	19 1
	Potatoes, chips	26 2
	Spinach, boiled	12 6
	Tomatoes, fried	8 6
Drinks		mEq per teaspoon
	Bovril	5 5
	Marmite	4 4

Food values have been obtained from McCance and Widdowson's tables *, in some instances average figures have been used

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* McCance, R A, and Widdowson E M (1946) The Chemical Composition of Food. *Med Res Coun Spec Rep Ser*, No 235

Appendix 3

SOME NORMAL VALUES

Renal Functional Capacity

Some Normal Values for Young Subjects, 1·73 sq m Surface Area

Renal plasma flow	612 ± 68 ml /min
Renal blood flow	Approximately 1,200 ml /min
Glomerular filtration rate	
1 Inulin clearance	112 ± 15 ml /min Adult males by age groups* 20–29 yrs 123 ± 16 ml /min 50–59 yrs 99 ± 15 ml /min 80–89 yrs 65 ± 20 ml /min
2 Creatinine clearance	Approximately the same as inulin
Urea clearance (at urine flows greater than 2 ml /min)	75 ml /min
Maximal Tubular Capacity (Tm)	
1. To reabsorb glucose	323 ± 64 mg /min
2 To secrete PAH	68 ± 11 mg /min
Ability to concentrate (Fluid deprivation)	800 to 1,200 m osmole/l (i e S G (1 022 to 1 032)
Ability to dilute	40 to 80 m osmole/l (i e S G 1 002)
Ability to excrete a water load of 1 litre	800 ml excreted in next 4 hours

* Shock, N W (1946) "Kidney function tests in aged males" *Geriatrics* 1, 232

Daily Urinary Excretions

Twenty-four hour output, on a mixed diet These figures are given only as a guide

Ammonia	30 to 60 mEq
Calcium	80 to 300 mg
Coproporphyrin, total	14 to 100 μg
Chloride	60 to 200 mEq
Creatine	
Children	up to 150 mg
Women	small amounts
Men	nil
Creatinine	0 8 to 1 8 g
Diastase	8,000 to 30,000 units
Glucose	16 to 132 mg
Potassium	80 to 200 mEq
pH	4 8 to 7 4
Sodium	80 to 200 mEq
Titratable Acid (Hydrogen ion)	20 to 30 mEq
Urea	16 to 35 g
Uric Acid	0 1 to 2 0 g
Urobilinogen	Less than 2 mg
Volume	1,000 to 2,000 ml

Plasma Contents

		Useful average
Albumin	4 0 to 5 7 g /100 ml.	4 8 g /100 ml
Albumin/Globulin Ratio	1·2/1 to 4/1	2/1
Bicarbonate (see Carbon Dioxide)		
Bilirubin (total)	Less than 0 8 mg /100 ml	
Calcium	Total . 9 0 to 11 mg /100 ml	10 mg /100 ml
	Diffusible . 3 6 to 5 6 mg /100 ml	
	Non-diffusible 2 8 to 6 1 mg /100 ml	
Carbon Dioxide	25 to 31 mEq /l.	27 mEq /l
Chloride	99 to 108 mEq /l.	103 mEq /l
Cholesterol	Total, 120 to 240 mg /100 ml	200 mg /100 ml
	Ester, 60 to 80% of total	70% of total
Creatine	0 2 to 0 6 mg /100 ml.	0 4 mg /100 ml
Creatinine	0 7 to 1 2 mg /100 ml	1 mg /100 ml
Diastase	90 to 160 units/100 ml	
Fibrin(ogen)	200 to 400 mg /100 ml	300 mg /100 ml.
Globulin	1 5 to 3 0 g 100 ml	2 4 g. 100 ml
Glucose *Capillary*	Fasting or noon, 80 to 120 mg 100 ml	100 mg 100 ml
Venous	About 10 mg /100 ml. lower	
Osmolarity	275–285 m osmole/l	280 m osmole/l
*p*H	7 30 to 7 50	7 40
Phosphatase *Alkaline*	King-Armstrong, 3 to 13 units/100 ml	
	Bodansky, 1 5 to 4 units/100 ml	
Acid	King-Armstrong-total, 1 to 5 units/100ml	
	King-Armstrong-formaldehyde stable,	
	0 to 4 units/100 ml	
Phosphorus (inorganic)	Adults, 2 4 to 4 5 mg /100 ml	4 mg /100 ml
	Children, 4 to 6 5 mg /100 ml	
Potassium	4 0 to 5 5 mEq /l.	5 mEq /l.
Sodium	137 to 148 mEq /l.	142 mEq /l.
Urea	15 to 35 mg /100 ml (adults)	25 mg /100 ml
	10 to 25 mg /100 ml. (pregnancy)	
Uric Acid	2 to 5 mg /100 ml	

Approximate Composition of Various Body Fluids

Figures for some important constituents are given, as a guide

Fluid	HCO_3 mEq /l	Cl mEq /l	P *mM /l.	Na mEq /l	K mEq /l	Protein g /l	Water g /l
Serum	25	100	2	142	4 3	70	940
Interstitial fluid	28	111	—	145	3 3	traces	993
Spinal fluid	21	125	—	147	2 8	0·3	993
Gastric juice	—	145	—	50	12	mucus	993
Bile	38	108	—	150	5	mucus	990
Pancreatic juice	110	40	—	140	5 0	mucus	993
Jejunal juice	30	110	—	138	5 0	mucus	993
Sweat†	—	40	—	42	—	—	993
Intracellular fluid Skeletal muscle amounts per kg of intracellular water	—	mEq /kg 3	mM /kg 107	mEq /kg 7	mEq /kg 155	g /kg 306	

* mM, or millimole, is the molecular weight in milligrams

† The composition of sweat may vary considerably.

Body Contents of Sodium and Potassium. Red Cell Mass and Fluid Volumes

	Man 70 *Kg*	*Woman* 57 *Kg*
Total exchangeable Sodium	2,950 mEq	2,250 mEq.
Total exchangeable Potassium	3,200 mEq	2,300 mEq
Plasma Volume	2 83 l	2 40 l
Red cell Mass	2 1 l	1·8 l.
Extra-cellular fluid	14 l	11 l
Intra-cellular fluid	25 l	20 l.
Total body water	39 l.	31 l.

Equivalent and Molecular Weights

Equivalent Weights

N	14	Mg	12
K	39	P	16 (variable)
Ca	20	Cl	35 5
Na	23	O	8

Molecular Weights.

Na Citrate ($2H_2O$)	294 0
Na Cl	58 5
Na Lactate	112 0
Na HCO_3	84 0
Na_2 HPO_4 ($12H_2O$)	358 2
Na H_2PO_4 ($2H_2O$)	156 0
K HCO_3	100 1
K Cl	74 6
K_3 Citrate (H_2O)	324 4
K Acetate	98 1
K_2 HPO_4	174 23
NH_4 Cl	53 5
Ca gluconate (H_2O)	448 4
Ca Cl_2	111 0
Ca Lactate ($5H_2O$)	308 3
Mannitol	180 0
Glucose	180·2

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